# Exhibit 30

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# DIMETHYLFORMAMIDE: PURIFICATION, TESTS FOR PURITY AND PHYSICAL PROPERTIES

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# DIMETHYLFORMAMIDE: PURIFICATION, TESTS FOR PURITY AND PHYSICAL PROPERTIES[+]

N,N'-Dimethylformamide (DMF) is a good solvent for organic and to a lesser extent inorganic compounds. It is, together with dimethylsulfoxide and acetonitrile, one of the most widely used of the so-called dipolar aprotic solvents. Owing to its fairly high dielectric constant, it is a moderately dissociating solvent for electrolytes. Acid-base reactions as well as thermodynamic properties of electrolyte solutions have been studied by many authors. Contrary to the N-methylamides it is a typically weakly associated solvent, as seen (Ref. 1) from dielectric studies (the Kirkwood g factor is about one at all temperatures).

Owing to its electron-donor character, DMF reacts with many acids. For example, Gutmann's donicity number (Ref. 2) is 27. Its polarographic range is quite large, e.g., 3.5 V at the dropping mercury electrode with 0.1 M $Bu_4NClO_4$ as supporting electrolyte (Ref. 3). It is therefore widely used as a solvent for electrochemical reactions, especially reductions.

Pure DMF is colorless and, at room temperature, odorless. It is subject to thermal as well as photochemical degradation. In presence of water, DMF is slowly hydrolyzed according to the equation:

$$HCON(CH_3)_2 + H_2O \longrightarrow HCOOH + (CH_3)_2NH$$

Formic acid and dimethylamine are thus predominant impurities in DMF and determine the odor of the impure solvent. They are weakly acidic and weakly basic respectively; therefore, partial ionization does occur:

$$HCOOH + (CH_3)_2NH \rightleftharpoons HCOO^- + (CH_3)_2NH_2^+$$

and results in a buffered solution (pH 11) with an increase in the conductivity of the solvent.

Thermal degradation produces dimethylamine and carbon monoxide. Hydrogen (Ref. 4) and hydrogen cyanide (Ref. 5) have been identified among the products of the photochemical degradation of the solvent.

Strongly basic media are difficult to obtain in DMF; there is, to our knowledge, no substance behaving as a strong base in DMF. If autoprotolysis of the medium actually occurs, the anion of the solvent must be very unstable (Ref. 6). It has been claimed (Ref. 7 and 8) that the autoprotolysis constant is smaller than $10^{-25}$ but no definite value has yet been proposed.

Attention must be paid to the fact that DMF has toxic effects, particularly on the liver and kidneys; the threshold value for air has been fixed (Ref. 9) at 30 $mg/m^3$.

## PURIFICATION OF DIMETHYLFORMAMIDE

Good quality DMF is commercially available. As noted by Vaughn (Ref. 10), spectrograde solvent is not always suitable for all purposes. As a consequence of hydrolysis, the residual water content of commercial DMF is frequently low (0.1%). Many procedures have been proposed and used for the purification of the solvent. Four types of successive operation can be distinguished: treatment with a drying agent, neutralization of basic or acidic impurities, careful distillation, and elimination of gaseous impurities.

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1. Preparing water-free solvent. Although the boiling point of water is far from that of DMF it is not possible to obtain a dry solvent by distillation only.

One of the first methods proposed for preliminary drying (Ref. 11) was azeotropic distillation with about 10% by volume of dry benzene; the benzene-water azeotrope is removed by distillation at atmospheric pressure. To prevent decomposition the temperature is maintained below 80°C. Alternatively, molecular sieves can be used. The solvent is kept in contact for periods ranging from 1 to 4 days with 4 Å (Ref. 12-15) or 5 Å (Ref. 16) sieves which are removed and replaced from time to time. Ritchie (Ref. 17) recommends the use of Linde AW-500 molecular sieves in 1/16-inch pellets. Studying drying efficiency, he finds that the water content is less than 18 ppm after 27 hours. Molecular sieves can be dried before use by heating in a quartz tube under a stream of argon at 375°C for 24 h (Ref. 18). Finally, a procedure which uses chromatographic purification through alumina has been described by Moe (Ref. 13) in some detail. "A column approximately 100 cm long and 5 cm wide will contain 1 kg of alumina, sufficient for the purification of about 10 l of DMF". After bubbling of pure nitrogen for several hours the DMF thus obtained is thought to be convenient for polarographic use.

In our opinion these three types of operation can be considered only as a first step in drying the solvent, and mild chemical drying agents must also be used. These range from anhydrous BaO (Ref. 11 and 19) to $MgSO_4$ (Ref. 20), $Na_2CO_3$ (Ref. 6 and 20), or $CuSO_4$ (Ref. 21). Surprisingly good samples of DMF can be obtained using storage of solvent over these chemicals for at least 24 h. It has been recommended that the drying agent be changed at least twice and the container shaken, if not continuously, at least from time to time. It also has been recommended that such an operation is performed in a cold, dark room. As far as $Na_2SO_4$ or $Na_2CO_3$ are concerned, the resulting solvents are of about the same quality (Ref. 20). Little or no degradation of the solvent (as estimated through the concentration of dimethylamine) results from such treatment (Ref. 11).

Some of the more common drying agents react with the solvent itself to produce significant amounts of acidic or basic impurities. BaO, cited previously, belongs to this category if it is used at temperatures above 30°C (Ref. 11). Other reagents are potassium hydroxide, calcium hydride (Ref. 5 and 22) and phosphorus pentoxide (Ref. 17, 23 and 24). $P_2O_5$ is the most frequently used, $CaH_2$ is probably the most efficient. Prue and Sherrington (Ref. 23) have shaken DMF for three days with $P_2O_5$, adding each morning about 10 g of fresh reagent. Recently, drying of amides using Vitrid, sodium bis(methoxy-2-ethoxy)aluminohydride, has been recommended (Ref. 25). In DMF it allows attainment of very basic media (pH 30). However, distillation of the solvent from the mixture obtained has not been attempted and is probably very hazardous. Whatever the method used, it is important to proceed with these operations in a dark room or apparatus to prevent any photochemical degradation.

2. Neutralization. Depending on the drying agent used, it has been recommended that the basic or acidic impurities produced are neutralised, either by shaking with picric acid (Ref. 20) or KOH pellets (Ref. 24). This last treatment is particularly recommended after drying over $P_2O_5$ which generates formic acid. Such neutralization can be done either before or after a first distillation.

3. Distillation. The drying process can be further carried out during this operation. The DMF is refluxed and distilled from $P_2O_5$ or $CaH_2$. However, owing to a degradation process increased by heating, it is preferable first to decant the solvent and transfer it under dry nitrogen, and then to distil it at reduced pressure.

The quality of the final product is greatly affected by the care with which the distillation is carried out. It seems to be important to work under vacuum, with a darkened column, or in a pure nitrogen or argon atmosphere. As a rule, the temperature must be kept under 60°C; heating must be gentle and overheating avoided. Distillation in daylight results in the production of hydrogen cyanide (Ref. 5), particularly in the presence of $CaH_2$. No traces of HCN are detected if the operations are conducted in the dark.

Types of distillation apparatus currently described in the literature do not seem to be very efficient. It is not surprising to note that the best quality DMF, if conductivity is accepted as a test of purity, has been obtained by Brummer (Ref. 12), who used only molecular sieves as drying agents, but carried out the distillation in a slow current of dry nitrogen at low pressure (2 torr) and an efficient column (1 meter packed with Fenske helices). The use of a long column (60 cm at least) with good packing and reflux is recommended. For example, Tanaka (Ref. 21) distilled DMF which had been dried over anhydrous $CuSO_4$ at a pressure of 5 torr through an adiabatic fractional distillation column which was 1.3 cm in diameter, 120 cm in length and packed with helipack coils. Dry nitrogen was passed through the apparatus during the distillation; 60% of the distillate was collected. The conductivity was lower than $1 \times 10^{-7}\ \Omega^{-1}\ cm^{-1}$ (25°C). Boiling temperatures at various pressures are given in Table 1.

TABLE 1. Recommended values for physical constants of DMF at 25°C and 1 atm (except where noted otherwise)

| | | |
|---|---|---|
| Boiling temperature | $T_B$ | 152.3°C (Ref. 47) |
| | | 79°C at 61-62 torr (Ref. 37) |
| | | 55-56°C at 25-26 torr (Ref. 40) |
| | | 34°C at 2-3 torr (Ref. 15) |
| Melting temperature | $T_M$ | -61°C |
| Refractive index (Ref. 44) | $n_D^{25}$ | 1.42689 |
| Dielectric constant | D | 37.0 |
| Surface tension (Ref. 45) | $\sigma$ | 37.1 dyne/cm |
| Viscosity (Ref. 23) | $\eta$ | 0.00796 poise |
| Density | $\rho$ | 0.9440 g $cm^{-3}$ |
| Molal volume | V | 77.39 $cm^3$ |
| Heat capacity at constant pressure (Ref. 44) | $C_p$ | 37.4 cal/mol |
| Cubic expansion coefficient | $\alpha_P$ | $1.00 \times 10^{-3}$ $K^{-1}$ * |
| Adiabatic compressibility coefficient (Ref. 44) | $\beta_S$ | $6.1 \times 10^{-5}$ $atm^{-1}$ |
| Isothermal compressibility coefficient | $\beta_T$ | $6.3 \times 10^{-5}$ $atm^{-1}$ * |

*Calculated from data in Ref. (12)

4. Elimination of gaseous impurities. A flow of pure dry nitrogen or argon is passed through the solvent for several hours, in order to eliminate oxygen, carbon monoxide and carbon dioxide. Such a solvent can then be used for polarographic purposes. A more complete deaeration can be achieved using a vacuum line.

5. Conclusions and recommendations. As various authors used different starting materials, it is difficult to compare the efficiency of the various methods of purification. Comparison between different ways of treating the same batch of solvent can be found to our knowledge in only two papers (Ref. 11 and 20). Thomas and Rochow (Ref. 11) always used first azeotropic distillation with benzene and compared subsequent treatment with $MgSO_4$, BaO, alumina and triphenylchlorosilane, followed in each case by distillation. Comparisons were made in terms of specific conductance and water content. Barium oxide as well as alumina treatment meet rather well these two criteria and do not have any side effects, such as producing dimethylamine or HCN. Juillard (Ref. 20) compared drying with $Na_2CO_3$, $Na_2SO_4$ or molecular sieves with azeotropic distillation with benzene and distillation over $P_2O_5$. As far as conductivity and water content are concerned, the different batches of solvent thus obtained were of about the same quality, except that $P_2O_5$ has the disadvantage of promoting degradation of the solvent and thus of decreasing the efficiency of the distillation; therefore the use of $P_2O_5$ is not recommended. As a confirmation it can be noted that authors using $P_2O_5$ or $CaH_2$ as drying agents did not obtain purer solvents than those who employed BaO or $Na_2CO_3$ or even only molecular sieves.

It is therefore recommended that use is made first either of azeotropic distillation with benzene, as suggested by Thomas (Ref. 11), or of treatment with molecular sieves, as suggested by Ritchie (Ref. 17), and that the resulting DMF is then shaken with $Na_2CO_3$ or, better, with BaO for 1 or 2 days. After decantation the DMF is distilled twice under nitrogen (pressure <15 torr) using a 1-m column. All these operations must be carried out in the dark. After deaeration the solvent is stored under nitrogen and used as soon as possible.

TESTS FOR PURITY

Owing to its various modes of degradation (hydrolysis, thermal and photochemical decomposition) the principal impurities found in DMF are: dimethylamine, formic acid, hydrogen cyanide, carbon dioxide and carbon monoxide. To this list must be added: water, oxygen, which is quite soluble, and impurities resulting from the purification process.

Conductivity. As stressed earlier, hydrolysis as well as decomposition results in ionic impurities: dimethylammonium formate, carbonate or cyanide. Thus, the conductivity of the solvent is a very good test of its purity.

Experimental conductivities recorded in DMF are always higher than those reported for other aprotic solvents such as ketones or nitriles. According to a rough estimate, the theoretical conductivity of the solvent should be below $10^{-13}$ $\Omega^{-1}cm^{-1}$. In fact, conductivities obtained by the most careful workers are scarcely ever less than $10^{-7}$. The best values have been reported, to our knowledge, by Brummer (Ref. 12) who used for conductometric studies a solvent having conductivities varying from $2 \times 10^{-8}$ to $5 \times 10^{-8}$ $\Omega^{-1}$ $cm^{-1}$. Values below $5 \times 10^{-7}$ have been reported by numerous authors and any batch of DMF which is more conducting can be considered to be impure.

Water. Water can be titrated by the Karl Fischer (K-F) reagent. Kanatharan (Ref. 22) recommends that the titration is conducted slowly, since K-F reagent reacts only slowly with small amounts of water.

Usual procedures do not allow the determination of less than 10 ppm of water. According to Muroi (Ref. 26) it is possible to titrate as little as 0.2 ppm by increasing the sharpness of the end point, using the following procedure: "Add a 10-30 ml sample to 25 ml MeOH containing 8% of a pyridine-$SO_2$ solution (320 g $SO_2$/l pyridine) and titrate potentiometrically with K-F reagent having a titre of 0.1-0.5 mg $H_2O$/ml". The use of DMF as a solvent for K-F reagent also has been advocated (Ref. 27).

Prue (Ref. 23) has titrated water in DMF using triphenylsilyl chloride, from which, according to Thomas (Ref. 11), hydrogen chloride is liberated quantitatively by water (amines or acids are thought to interfere); the HCl content is then estimated from the conductivity of the solution.

It is quite easy to prepare a solvent which contains less than 50 ppm of water. Very low concentrations (< 5ppm) are more difficult to attain. The best value, less than 3 ppm, has been reported by Libbey and Stock (Ref. 28).

Dimethylamine. Colorimetric methods have been used by some authors. In our opinion, as long as the autoprotolysis constant of the solvent is not known, it is not possible to say exactly what is basic and what is acidic in DMF. Kolthoff (Ref. 24) has used p-nitrophenol in the colorimetric determination of total basicity, but specific determinations would be preferable.

Thomas and Rochow (Ref. 11) have based the determination of the amine content on the fact that dimethylamine forms with 1-fluoro-2,4-dinitrobenzene a complex which absorbs in the visible spectrum at 3812 Å. Solvent prepared by Chang and Criss (Ref. 29) was found to contain less than 1 ppm of dimethylamine using this method.

Another spectrophotometric method which allows the determination of the dimethylamine content down to 2 ppm with an error of $\pm$10% has been proposed by Pribyl (Ref. 30); dimethyldithiocarbamate, which absorbs at 445 nm, is formed by adding $CS_2$ and $Cu(AcO)_2$ to an EtOH-pyridine mixture.

Chromatography was thought by Butler (Ref. 18) not to be a reliable means of establishing the organic impurity content of the solvent since DMF can decompose or hydrolyze at high temperatures. Nevertheless, careful studies of the proper experimental conditions have been undertaken (Ref. 31 and 32). In the paper by Filippov (Ref. 32) it is shown that dimethylamine can be determined in DMF at levels as low as 1 ppm using tetrahydroxyethylenediamine as a stationary phase, polysorb-1 as a solid support and a column temperature of 75°C.

Dimethylamine is not electroactive with mercury but can give coordination compounds with cations which will affect the course of electrochemical reductions.

Formic Acid. In contrast to dimethylamine, formic acid is electroactive. Kanatharan and Spritzer (Ref. 22) have attributed to formic acid two peaks, one cathodic, the other anodic, which appear in cyclic voltammograms of aqueous dimethylformamide. Alternating current polarography (Ref. 33), and, better, pulse polarography, can be used to estimate the formic acid content.

Formic acid can also be determined by titration with a base. Potentiometric titration is preferred since it allows determination of the dimethylammonium formate content as well. Megliskii (Ref. 34) has titrated potentiometrically formic acid, dimethylamine and dimethylammonium formate in DMF using two solutions: 0.1 M $HClO_4$ and 0.1 M KOH, both in alcohol. Such a method is suitable only for concentrations of the order of at least 100 ppm.

Hydrogen Cyanide. Trisler et al. (Ref. 5) reported the presence of HCN in DMF distilled over $CaH_2$ in natural light. Concentrations ranged from $10^{-5}$ to $10^{-3}$ M. Spectrophotometric titration can be carried out with 4-nitrobenzil, which reacts with cyanide ion to form a deep violet ion.

Oxygen. Oxygen is rather soluble in DMF. A study of oxygen solubility in relation to the oxygen content of the gas phase has been made by James (Ref. 35). When the gas phase was air and pure oxygen, the solubility was 2.2 x $10^{-3}$ and 3.1 x $10^{-3}$ M, respectively.

Oxygen is an electroactive impurity which interferes in polarography and other electrochemical processes. Two waves are observed (Ref. 36) with $E_{1/2}$ = -0.8 and -2.8 V vs. SCE; the first corresponds to the reduction of oxygen to superoxide:

$$O_2 + e^- \longrightarrow O_2^{\cdot -}$$

and the second one to the reduction of superoxide to peroxide ion:

$$O_2^{\cdot -} + e^- \longrightarrow O_2^{=}$$

James (Ref. 35) has proposed two methods for the determination of the oxygen concentration; polarography and the Winkler method. Polarographic measurements are made at -1.2 V vs. SCE, in order to ensure that the measured diffusion current is not influenced by a polarographic maximum. A modified Winkler method allows concentrations as low as 10 ppm to be determined. It depends upon quantitative oxidation of iodide ion to iodine. Such a process is described in some detail (Ref. 35).

## PHYSICAL PROPERTIES OF DIMETHYLFORMAMIDE

Numerical values of physical constants are highly dependent on the purity of the solvent. Consequently, important discrepancies are found in the literature. The present recommended values result from a careful examination of three aspects: accuracy of the measurements, consistency of the data of various authors at different temperatures, and purification of the solvent. Such a choice is subject to personal evaluation and it seems prudent to give also the other references.

Density. The density is probably a good criterion of the purity of the solvent. Contamination with water increases the density (Ref. 23). The following values of the density at 25°C have been found (Ref. 23,8,37,12): 0.9439, $0.9440_2$, $0.9441_5$ and 0.9442 g $cm^{-3}$, respectively. Old values greater than 0.9443 frequently found in tables are probably too high. New work by Kawaizumi and Zana (Ref. 38) seems to indicate that the density of the pure solvent is lower. These authors obtain values ranging from 0.94360 to 0.94368. It is our feeling that these data are more accurate than previous ones but such a low value ($\rho$ = 0.94364 $\pm$ 0.00004) must be confirmed by others before being accepted.

Values at various temperatures other than those appearing in Table 2 have been given by Gopal and Rizvi (Ref. 39). At 20°C Saphon (Ref. 40) has obtained $\rho$ = 0.94878 g $cm^{-3}$, in good agreement with the value in Table 2.

TABLE 2. Recommended values for physical constants of DMF at various temperatures

| | | $\rho$ g $cm^{-3}$ | $\eta$ poise | D |
|---|---|---|---|---|
| Temperature | 20°C | 0.9488 | 0.00845 | 38 |
| | 30°C | 0.9394 | 0.00746 | 36.1 |
| | 40°C | 0.9298 | 0.00664 | 34.4 |
| | 50°C | 0.9202 | 0.00598 | 32.8 |
| Reference | | 12 | 49 | 1 |

Viscosity. Other values can be found in References (29) and (41). Prue's data at 25°C are confirmed by measurements reported by Ames and Sears (Ref. 42).

Dielectric constant. Data given by Bass and Cole (Ref. 1) are preferred to previous results (Ref. 43) of Leader and Gormley (36.71 at 25°C). The value reported at 25°C is interpolated from measurements at various temperatures. Data of Saphon (Ref. 40) are in good agreement with the value reported in Table 2 at 20°C (D = 38.13).

Miscellaneous. Data at various temperatures concerning refractive index, surface tension and isothermal compressibility can be found in Refs. (44), (45) and (12), respectively. Other data concerning thermodynamic properties are reported in Refs. (39) and (44). Plots of vapor pressure, heat of vaporization, heat capacity, density, viscosity, surface tension and thermal conductivity for a large range of temperature have been drawn up by Gallant (Ref. 46). The solubilities of some sixty substances in DMF have been tabulated (Ref. 50). Organic reactions in or with DMF have been summarized (Ref. 51).

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# Exhibit 31

# FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

*Get updates on the recalls*

### Update: 11/13/2019 - FDA warns Mylan for CGMP deviations

**Update [11/13/2019]** Today, the U.S. Food and Drug Administration posted a warning letter (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019) to Mylan Pharmaceuticals, Inc. in Chodavaram Village, Vizianagaram, Andhra Pradesh, India. Mylan manufactures valsartan active pharmaceutical ingredient (API) and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several current good manufacturing practice (CGMP) deviations at this Mylan facility, including failure to have adequate written procedures for the receipt, identification and handling of raw materials and failure to adequately clean equipment and utensils. Failure to correct these deviations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

### Update: 10/15/2019 - FDA warns Torrent for CGMP violations

**Update [10/15/2019]** Today, the U.S. Food and Drug Administration posted a warning letter (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019) to Torrent Pharmaceuticals in Ahmedabad, Gujarat, India. Torrent manufactures losartan potassium tablets and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several manufacturing violations at Torrent's Taluka-Kadi, Indrad, Gujarat facility, including failure to follow written procedures for production and process control and failure to adequately investigate batch discrepancies. Failure to correct these violations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

**Update: 9/20/2019 - Torrent expands its voluntary recall of losartan**

**Update [9/20/2019]** Torrent Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-0) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.
The agency updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

**8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications**

Go to FDA Statement (/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications)

**6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA**

**Update [6/26/2019]** FDA is alerting patients and health care professionals to Macleods Pharmaceuticals' voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/macleods-pharmaceutical-limited-issues-voluntary-nationwide-consumer-level-recall-losartan-potassium) of two lots of losartan potassium tablets (50mg strength) and 30 lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets (12 lots of 50mg/12.5mg strength, three lots of 100mg/12.5mg strength, and 15 lots of 100mg/25mg strength). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs). The agency also updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) .

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

### 6/12/2019: UPDATE - Teva expands its voluntary recall of losartan

**Update [6/12/2019]** Teva Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-expands-voluntary-nationwide-recall-losartan-potassium-50-mg-and-100-mg) to include seven additional lots of losartan potassium tablets (three lots of 50 mg strength and four lots of 100 mg strength) labeled by Golden State Medical Supply. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

**5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA**

**Update [5/6/2019]** FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/vivimed-life-sciences-pvt-ltd-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-50-mg-and) of 19 lots of losartan potassium tablets made by Vivimed Life Sciences Pvt Ltd in Alathur, Chennai, India and distributed by Heritage Pharmaceuticals Inc, East Brunswick, New Jersey, due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). Vivimed is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2) of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

The agency also updated the list of recalled ARBs (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

**5/2/2019: UPDATE - Laboratory analysis of valsartan products**

**Update [5/2/2019]** FDA posted laboratory test results showing NDEA levels in recalled valsartan products (/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) as well as an assessment of the cancer risk from NDEA in valsartan.

**4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA**

**Update [4/29/2019]** FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg) of 44 lots of losartan potassium tablets manufactured by Teva Pharmaceuticals and labeled as Golden State Medical Supply due to the detection of the impurity N-Nitroso-N-methyl-4-

aminobutyric acid (NMBA). The recalled products were made with active pharmaceutical ingredient (API) manufactured by Hetero Labs. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.
Additionally, Legacy expanded its recall (/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets) to include one additional lot of losartan tablets made with API manufactured by Hetero Labs.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

The agency also updated the list of recalled losartan medicines (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

**4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods**

**Update [4/19/2019]** Torrent Pharmaceuticals Limited is further expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium) to include 104 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.
The agency updated the list of losartan products under recall (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

FDA is also posting new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A direct injection GC-MS method (/media/123409/download) that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine

(NEIPA), and N-nitrosodibutylamine (NDBA)

- A headspace GC-MS method (/media/124025/download) that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

**4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue**

Go to FDA Statement (/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys)

**3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information**

**Update [3/22/2019]** FDA has updated the list of valsartan medicines under recall (/media/118231/download) to incorporate additional repackagers of Aurobindo's valsartan-containing medicine. FDA has also updated the list of losartan medicines under recall (/media/119422/download) to include repackagers of Torrent's and Camber's losartan-containing medicines.

The agency also updated the list of valsartan medicines not under recall (/media/118232/download) accordingly.

**3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market**

**Update [3/20/2019]** To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the interim acceptable intake limit of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated. The agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the U.S. supply in approximately six months.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

FDA reminds patients taking recalled losartan to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death. Untreated diabetic nephropathy (kidney disease) leads to worsening renal (kidney) disease.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA continues to work with companies and international regulators to ensure products entering the U.S. market do not contain nitrosamine impurities.

**3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan**

**Update [3/1/2019]** Torrent Pharmaceuticals Limited is further expanding its voluntary recall (https://public4.pagefreezer.com/browse/FDA/02-07-2022T12:48/https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium-0) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) to include 114 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Today, the agency also issued a press release (https://public4.pagefreezer.com/browse/FDA/28-06-2022T09:52/https://www.fda.gov/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-arb-drug-products-reports-finding-new-nitrosamine) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) to provide additional information about its ongoing investigation and another voluntary recall by Hetero/Camber

Pharmaceuticals, which was announced on February 28, of 87 lots of losartan potassium tablets (25 mg, 50 mg and 100 mg). The recalled losartan potassium and losartan potassium/hydrochlorothiazide tablets are also manufactured by Hetero, which are distributed by Camber, and contain the impurity NMBA.

Torrent and Hetero/Camber are only recalling lots of losartan-containing medication with NMBA above the interim acceptable intake limits of 0.96 parts per million (ppm).

The agency also updated the list of losartan products under recall (/media/119422/download).

### 3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan

**Update [3/1/2019]** AurobindoPharma USA is expanding its voluntary recall (AurobindoPharma USA, Inc. Initiates a Voluntary Nationwide Consumer Level Recall Expansion of 38 Lots of Amlodipine Valsartan Tablets USP and Valsartan Tablets, USP due to the detection of NDEA (N-Nitrosodiethylamine) Impurity.) to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine.

Aurobindo is only recalling lots of valsartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.083 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the valsartan products under recall (/media/118231/download).

### 3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall

Go to Press Release (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632425.htm)

### FDA updates table of interim limits for nitrosamine impurities in ARBs

**Update [2/28/2019]** FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

### Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

| Drug | Maximum Daily Dose (mg/day) | Acceptable Intake NDMA (ng/day)* | Acceptable Intake NDMA (ppm)** | Acceptable Intake NDEA (ng/day)* | Acceptable Intake NDEA (ppm)** | Acceptable Intake NMBA (ng/day)* | Acceptable Intake NMBA (ppm)** |
|---|---|---|---|---|---|---|---|
| **Valsartan** | 320 | 96 | 0.3 | 26.5 | 0.083 | 96 | 0.3 |
| **Losartan** | 100 | 96 | 0.96 | 26.5 | 0.27 | 96 | 0.96*** |
| **Irbesartan** | 300 | 96 | 0.32 | 26.5 | 0.088 | 96 | 0.32 |
| **Azilsartan** | 80 | 96 | 1.2 | 26.5 | 0.33 | 96 | 1.2 |
| **Olmesartan** | 40 | 96 | 2.4 | 26.5 | 0.66 | 96 | 2.4 |
| **Eprosartan** | 800 | 96 | 0.12 | 26.5 | 0.033 | 96 | 0.12 |
| **Candesartan** | 32 | 96 | 3.0 | 26.5 | 0.83 | 96 | 3.0 |
| **Telmisartan** | 80 | 96 | 1.2 | 26.5 | 0.33 | 96 | 1.2 |

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure
** These values are based on a drug's maximum daily dose as reflected in the drug label
*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

**2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled**

**Update [2/25/2019]** FDA is alerting patients and health care professionals to a voluntary recall of one lot of losartan potassium/hydrochlorothiazide (HCTZ) 100mg/25mg combination tablets manufactured by Macleods Pharmaceuticals. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine made with active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Macleods is only recalling lots of losartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.27 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the list of losartan products under recall (/media/119422/download).

**1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues**

Go to FDA Statement (/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps)

**1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan**

**Update [1/23/2019]** Torrent Pharmaceuticals is further expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) to include six additional lots of losartan potassium and hydrochlorothiazide combination tablets, for a total of 16 lots of losartan-containing medicines. This recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan-containing medication containing NDEA above the interim acceptable intake limits of 0.27 parts per million (ppm).

The agency also updated the list of losartan medications under recall (/media/119422/download).

**1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled**

**Update [1/18/2019]** FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-irbesartan-and-irbesartan-hctz) of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Prinston Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the irbesartan active pharmaceutical ingredient manufactured by Zhejiang Huahai Pharmaceuticals (ZHP).

Solco is only recalling lots of irbesartan-containing medication where NDEA has been detected above the interim limit of 0.088 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin receptor II blockers (ARBs).

The agency also updated the list of irbesartan products under recall.

### 1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan

**Update [1/3/2019]** Torrent Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp) to include eight additional lots of losartan potassium tablets, for a total of 10 lots. This recall is due to trace amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan medication containing NDEA above the interim acceptable intake level of 0.27 parts per million.

The agency also updated the list of list of valsartan products under recall (/media/118231/download).

### 1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA

**Update [1/2/2019]** FDA is alerting patients and health care professionals to Aurobindo Pharma USA's voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lots-amlodipine) of two lots of valsartan tablets, 26 lots of amlodipine and valsartan combination tablets, and 52 lots of valsartan and hydrochlorothiazide (HCTZ) combination tablets due to the amount of N-Nitrosodiethylamine (NDEA) in the valsartan active

pharmaceutical ingredient. Aurobindo is recalling amlodipine and HCTZ only in combination medications containing valsartan. Neither amlodipine nor HCTZ is currently under recall by itself.

Aurobindo is recalling lots of valsartan-containing medication that tested positive for NDEA above the interim acceptable daily intake level of 0.083 parts per million.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above interim acceptable daily intake levels.

FDA also updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download).

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Some ARBs contain no NDMA or NDEA.

**12/20/2018: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA**

**Update [12/20/2018]** FDA is alerting patients and health care professionals to Torrent Pharmaceuticals' voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) of two lots of losartan potassium 100 mg tablets due to N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Not all Torrent losartan-containing medications distributed in the U.S. are being recalled. Torrent is recalling only those lots of losartan medication that tested positive for NDEA above the acceptable daily intake of 0.27 ppm.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable daily intake levels.

FDA posted a list of losartan medications under recall (/media/119422/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain

NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

### 12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs

**Update [12/19/2018]** FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

The agency evaluated safety data for N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) to determine an interim acceptable intake level for these impurities in the ARB class. NDMA and NDEA are probable human carcinogens and should not be present in drug products. We are currently aware of NDMA and NDEA in certain valsartan, irbesartan and losartan-containing products, and those products and some active pharmaceutical ingredients (API) used to manufacture them have been recalled from the U.S. market. See the list of valsartan products under recall (/media/118231/download) and the list of irbesartan products under recall (/media/118233/download).

Drug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients. The agency will use the interim limits to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects a new impurity or higher level of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients. To aid industry and regulatory agencies, FDA has developed and published methods to detect NDMA and NDEA impurities – the gas chromatography/mass spectrometry (GC/MS) headspace method (/media/115965/download), the combined GC/MS headspace method (/media/117843/download), and the combined GC/MS direct injection method (/media/117807/download). These methods can be used for drug substances and products, and users should validate them as part of good manufacturing practices and where data are used to support a regulatory submission or required quality assessment of the API or drug product.

Not all ARB products contain NDMA or NDEA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

### Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

| Drug | Maximum Daily Dose (mg/day) | Acceptable Intake NDMA (ng/day)* | Acceptable Intake NDMA (ppm)** | Acceptable Intake NDEA (ng/day)* | Acceptable Intake NDEA (ppm)** |
|---|---|---|---|---|---|
| **Valsartan** | 320 | 96 | 0.3 | 26.5 | 0.083 |
| **Losartan** | 100 | 96 | 0.96 | 26.5 | 0.27 |
| **Irbesartan** | 300 | 96 | 0.32 | 26.5 | 0.088 |
| **Azilsartan** | 80 | 96 | 1.2 | 26.5 | 0.33 |
| **Olmesartan** | 40 | 96 | 2.4 | 26.5 | 0.66 |
| **Eprosartan** | 800 | 96 | 0.12 | 26.5 | 0.033 |
| **Candesartan** | 32 | 96 | 3.0 | 26.5 | 0.83 |
| **Telmisartan** | 80 | 96 | 1.2 | 26.5 | 0.33 |

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer
risk after 70 years exposure
** These values are based on a drug's maximum daily dose as reflected in the drug label

For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.

### 12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter

**Update [12/12/2018]** The FDA has updated its testing methods to detect NDMA and NDEA impurities – the ( ([!--$ssDownloadLink('UCM618053')--])GC/MS) headspace method (/media/115965/download), the combined headspace method (/media/117843/download), and the combined direct injection method (/media/117807/download) – by adding the limits of detection (LOD) and clarifying that the methods can be used for both drug substances and drug products. These methods were

validated with respect to valsartan drug substances and drug products, but the agency expects them to have comparable LODs and limits of quantitation (LOQ) for other angiotensin II receptor blockers (ARB).

The agency also issued a press release announcing the posting of a warning letter the agency issued Nov. 29 to Zhejiang Huahai Pharmaceuticals Co. Ltd. (ZHP).

**12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications**

Go to Press Release (/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these)

**12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products**

**Update [12/6/2018]** Mylan Pharmaceuticals is expanding its voluntary recall ([!--$wcmUrl('link','UCM627647')--])to include all lots of non-expired valsartan-containing products due to trace amounts of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient (API) manufactured by Mylan Laboratories Limited. The 104 additional lots include 26 lots of amlodipine and valsartan tablets, 51 lots of valsartan tablets and 27 lots of valsartan and hydrochlorothiazide tablets. These lots were distributed in the U.S. between March 2017 and November 2018.

The agency also updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download).

**11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA**

**Update [11/27/2018]** FDA is alerting patients and health care professionals to Teva Pharmaceuticals' voluntary recall (/safety/recalls-market-withdrawals-safety-alerts) of valsartan-containing products manufactured using active pharmaceutical ingredient (API) from Mylan Pharmaceuticals. Mylan voluntarily recalled (/safety/recalls-market-withdrawals-safety-alerts) valsartan-containing products on November 20.

Teva is recalling all lots of amlodipine and valsartan combination tablets and amlodipine, valsartan, and hydrochlorothiazide (HCTZ) combination tablets due to the presence of N-Nitrosodiethylamine (NDEA). Teva has recalled other valsartan-containing products in

recent months due to the presence of N-Nitrosodimethylamine (NDMA). With this recall, Teva has now recalled all their unexpired valsartan-containing products from the U.S. market.

The agency continues to investigate and test all angiotensin II receptor blocker (ARBs) for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download). The agency reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

### 11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA

**Update [11/21/2018]** FDA is alerting patients and health care professionals to Mylan Pharmaceuticals' voluntary recall of 15 lots of valsartan-containing products due to the presence of N-Nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the U.S. are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of valsartan products under recall (/media/118231/download)and valsartan products not under recall (/media/118232/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

### 11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan

**potassium and hydrochlorothiazide recall of one lot due to NDEA**

**Update [11/9/2018]** FDA is alerting patients and health care professionals to Sandoz's voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-voluntary-nationwide-recall-one-lot-losartan-potassium-and-hydrochlorothiazide-due) of one lot – JB8912 – of losartan potassium and hydrochlorothiazide 100mg/25mg tablets, that contain losartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a diuretic, used in combination for the treatment of hypertension. Sandoz's product was made using an active pharmaceutical ingredient (API) that has tested positive for NDEA. The API was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd, which is on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html).

Sandoz's losartan drug products make up less than 1 percent of the total losartan drug products in the U.S. market.

FDA continues to investigate the presence of NDEA and NDMA, which are probable human carcinogens, in ARBs and is taking swift action when it identifies unacceptable impurities in API and finished drug products.

FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDEA or NDMA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

**10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA**

*Certain irbesartan products labeled as Westminster Pharmaceuticals Inc. and GSMS Inc. recalled*

**Update [10/30/2018]** FDA is alerting patients and health care professionals to ScieGen's voluntary recall of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain N-Nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen (causes cancer). FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply, Inc. (GSMS). See the list of irbesartan products under recall (/media/117814/download). This is the first non-valsartan drug product the agency has found to contain the NDEA impurity.

ScieGen's recall affects about 1 percent of the irbesartan drug products in the U.S. market.

Additionally, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is recalling (/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of their irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or N-Nitrosodimethylamine (NDMA), a probable human carcinogen previously found in certain recalled valsartan products, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA. FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The combined headspace method (/media/117843/download) and the combined direct injection method (/media/117807/download) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers to ensure their products are not at risk for NDMA or NDEA formation. The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

For additional information about ARB products, see:

- list of valsartan products under recall (/media/118231/download)
- list of valsartan products not under recall (/media/118232/download)

**10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information**

**Update [10/24/2018]** FDA continues to evaluate valsartan-containing products and other angiotensin II receptor blockers (ARBs), and has updated the list of products included in the recall (/media/118231/download) to add one additional lot of RemedyRepack.

### 10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method

**Update [10/16/2018]** FDA is posting a gas chromatography-tandem mass spectrometry (GC-MS/MS) method (/media/117807/download) utilizing liquid injection for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

This method provides an additional option for regulators and industry to detect NDMA and NDEA impurities. This method can be used alone or in combination with the combined gas chromatography-mass spectrometry (GC/MS) headspace method (/media/117843/download) the agency recently posted. Like the previously posted methods, this method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

### 10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA

**Update [10/11/2018]** ] FDA is posting a redeveloped combined gas chromatography-mass spectrometry (GC/MS) headspace (/media/117843/download) method for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

FDA previously posted a GC/MS method for detection of NDMA in valsartan products. Upon detection of NDEA in valsartan products manufactured by Zhejiang Huahai Pharmaceuticals, FDA redeveloped the testing method so that it can be used to detect and quantify levels of both NDMA and NDEA. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

FDA is also working on a GC/MS direct injection method for detection of NDMA and NDEA. We will post the method when it is available. This will provide an additional option for regulators and industry to use to detect both impurities.

### 10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products

**Update [10/5/2018]** FDA posted laboratory test results showing NDMA levels in recalled valsartan products. FDA will also post test results (/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) and an assessment of the cancer risk from NDEA when they are available.

**9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert**

**Update [9/28/2018]** FDA placed Zhejiang Huahai Pharmaceuticals on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html) on September 28, 2018, to protect U.S. patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent inspection (/media/117875/download) at ZHP's facility.

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

**9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan**

**Update [9/24/2018]** FDA has updated the list of valsartan products not under recall (/media/118232/download) with five Teva products that were not previously on either list.

**9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products**

Go to Press Release (/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional)

**8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings**

Go to FDA Statement (/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current)

**8/24/2018: UPDATE - FDA updates recall lists**

**Update [8/24/2018]** Torrent Pharmaceuticals Limited is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall). FDA has updated the list of valsartan products under recall (/media/118231/download).

**8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan**

**Update [8/22/2018**] Torrent Pharmaceuticals Limited is expanding its voluntary recall to all lots of unexpired valsartan-containing drug products due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals.

RemedyRepack, a repackager of Torrent's valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets, has also recalled.

FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products not under recall (/media/118232/download).

Additionally, FDA is releasing a gas chromatography-mass spectrometry (GC/MS) headspace method (/media/115965/download) for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. The agency is using this method to test potential NDMA-containing APIs and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

**8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods**

**Update [8/20/2018]** FDA is alerting health care professionals and patients that Torrent Pharmaceuticals Limited is voluntarily recalling (/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets) 14 lots of valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets. Not all Torrent valsartan products distributed in the U.S. are being recalled.

FDA recently learned Torrent used affected valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. FDA testing confirmed NDMA in some Torrent products.

To date, Torrent has not received any reports of adverse events related to this recall.

FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products not under recall (/media/118232/download) to incorporate additional repackagers of Camber's valsartan products and Torrent's recall.

NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.

**Estimated Range of Daily NDMA Consumption for certain foods (Recommended daily food consumption rates based on Dietary Guidelines for Americans 2015-2020 (https://health.gov/dietaryguidelines/2015/guidelines/))**

- Cured meat - 0.004-0.23 micrograms[1]
- Smoked meat - 0.004-1.02 micrograms[1]
- Grilled meat - 0.006-0.13 micrograms[1]
- Bacon - 0.07-0.09 micrograms[2]
    - In more ordinary terms, for example, one pound of bacon may contain 0.304-0.354 micrograms of NDMA

FDA reminds patients taking valsartan from a recalled lot that they should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. Not all valsartan products contain NDMA, so pharmacists may be able to provide a refill of valsartan medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

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[1] *Mavelle, T., B. Bouchikhi, and G. Debry, The occurrence of volatile N-nitrosamines in French foodstuffs. Food Chemistry, 1991. 42(3): p. 321-338.*

[2] *Park, J., et al., Distribution of Seven N-Nitrosamines in Food. Toxicol Res, 2015. 31(3): p. 279-288.*

**8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information**

**Update [8/9/2018]** FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products *not* under recall (/media/118232/download) to incorporate recalls of valsartan-containing products manufactured by Hetero Labs Limited, in India, labeled as Camber Pharmaceuticals Inc. Not all Camber valsartan products distributed in the U.S. are being recalled.

Camber Pharmaceuticals is recalling (/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg) certain valsartan tablets because they contain the impurity N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient (API). Hetero Labs manufactures the API for the Camber products using a process similar to Zhejiang Huahai Pharmaceuticals.

Test results from Hetero Labs show the amount of NDMA found in its valsartan API exceeds acceptable levels; although it is generally lower than the amount discovered in the API manufactured by Zhejiang.

FDA is testing samples of valsartan API and finished products to confirm the extent and amount of NDMA and help inform the ongoing investigation. The agency has also contacted other manufacturers of valsartan API to determine if their manufacturing processes are at risk for the formation of NDMA, and is working with them to ensure NDMA is not present in future valsartan API.

Valsartan is an angiotensin II receptor blocker (ARB), and FDA is investigating whether other types of ARBs are at risk for the presence of NDMA.

Recalled valsartan products labeled as Camber may be repackaged by other companies. FDA will provide updates as more information becomes available.

**8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities**

**Update [8/2/2018]** FDA continues to evaluate valsartan-containing products and has updated the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download). In addition to updating the lists, FDA revised information related to A-S Medication on the list of products included in the recall. The agency will continue to provide information when it becomes available.

FDA is working with drug manufacturers to ensure future valsartan active pharmaceutical ingredients (APIs) are not at risk of NDMA formation. The agency reminds manufacturers to thoroughly evaluate their API manufacturing processes, and changes to those processes,

to detect any unsafe impurities. If a manufacturer detects new or higher levels of impurity, they should take action to prevent changes to the product's safety profile.

**7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information**

**Update [7/27/2018]** FDA is updating health care professionals and patients after discovering that several additional companies that repackage drug products are also recalling valsartan-containing products.

FDA has product recall information from three additional repackagers of valsartan-containing products made by Teva Pharmaceuticals and Prinston Pharmaceuticals Inc. – labeled as A-S Medication Solutions LLC, AvKARE and RemedyRepack – and the agency has added them to the recalled products list. Two of these companies, A-S Medication and RemedyRepack, may also distribute valsartan products not affected by the recall. The agency is confirming this information and will provide an update once it is available.

The following additional repackagers are recalling or are expected to recall valsartan-containing products. FDA is working to gather product recall information from these companies and has removed them from the list of products that are not impacted by this recall:

- Bryant Ranch Prepack Inc.
- H. J. Harkins Company Inc. *(this company was not originally included on either list)*
- Lake Erie Medical, doing business as Quality Care Products LLC
- NuCare Pharmaceuticals Inc.
- Northwind Pharmaceuticals
- Proficient Rx

It is possible that not all valsartan-containing products repackaged by these companies are impacted by the recall. **FDA continues to evaluate valsartan-containing products** and will update the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download) as more information becomes available.

**7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.**

**Update [7/27/2018]** On July 13th, FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA). Valsartan is a medication commonly used to treat high blood pressure and heart failure.

NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches. Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen (https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf)—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods[1]. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion[2]. It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.

The amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. The agency wanted to put some context around the actual potential risk posed to patients who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, some levels of the impurity may have been in the valsartan-containing products for as long as four years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people. This assessment led to FDA's decision to have these batches recalled.

Patients taking valsartan from a recalled batch should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. It is important to know that not all valsartan products contained NDMA, so pharmacists may be able to provide a refill of valsartan medication from batches that that are not affected by the recall, or doctors may prescribe a different medication that treats the same indications.

**FDA continues to evaluate the safety of valsartan-containing products** and will update the list of products included in the recall (/media/118231/download) and the list of products not included in the recall (/media/118232/download) as more information becomes available. If you are taking a valsartan product, be sure to check to back as the lists may change.

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[1] *From Toxnet: https://toxnet.nlm.nih.gov/ (https://toxnet.nlm.nih.gov/)*

***Average Daily Intake:*** *WATER: (assume 3 to 6 ng N-nitrosodimethylamine/l)(1) 6 to 12 ng; direct intake from drinking water is probably much less than 1 ug/day(2). FOOD: (assume <0.1 to="" 84="" ug/kg)(4)=""><0.16 to="" 134="">*
*[(1) Kimoto WI et al; Water Res 15: 1099-1106 (1981) (2) USEPA; Ambient Water Quality Criteria Doc: Nitrosamines p.C-14 (1980) EPA 440/5-80-064 (4) IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 17: 125-76 (1978)]*

[2] *The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf (http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf))*

**7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall**

**Update [7/24/2018]** FDA is updating health care professionals and consumers on the agency's progress in responding to the ongoing recalls of valsartan, which is used to treat high blood pressure and heart failure, due to the presence of NDMA. The agency has posted a list of valsartan-containing products not impacted (/media/118232/download) by this recall. **FDA continues to evaluate valsartan-containing products** and will update the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download) as more information becomes available.

Manufacturers of these products often produce multiple dosage strengths, however not all of them are being recalled. FDA recommends health care professionals and patients carefully check these lists. Health care professionals and patients should check this statement frequently for any updates.

FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death.

Consumers and health care professionals should continue to report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178

**7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls**

**[7/18/2018]** The U.S. Food and Drug Administration is updating health care professionals and consumers following a recent FDA press release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity) about voluntary recalls of several drug products containing the active pharmaceutical ingredient (API) valsartan. Valsartan is used to treat high blood pressure and heart failure. Not all products containing valsartan are being recalled, and this update will clarify which valsartan-containing products are being recalled.

The recalled products contain an impurity, N-nitrosodimethylamine (NDMA), in the API manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

**The investigation into valsartan-containing products is ongoing, and the following list may change. We will update this statement as we have more information.**

There are currently three voluntary recalls related to the NDMA impurity detected in the valsartan API:

- **Teva Pharmaceuticals USA labeled as Major Pharmaceuticals —** recall is at the **retail level** because these products are only used in facilities where they are directly administered to patients by health care professionals: Valsartan 80 mg and 160 mg products;

- **Prinston Pharmaceuticals Inc. labeled as Solco Healthcare LLC —** recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products; and
- **Teva Pharmaceuticals labeled as Actavis LLC —** recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products.

Detailed list of products included in the recall (/media/118231/download) (PDF - 87 KB)

**What should patients know:**

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Not all valsartan-containing medications are affected and being recalled.
- If you are taking any medication containing valsartan, compare the information on your prescription bottle with the information in this list (/about-fda/page-not-found) (company, National Drug Code, lot number) to determine if your current medicine has been recalled. If you are not certain, contact your pharmacist.
- If you have medicine included in the recall, contact your pharmacist. The pharmacist may be able to provide you with valsartan made by another company. If not, contact your doctor immediately to discuss other treatment options.

**What health care professionals should know:**

- FDA has determined the recalled valsartan products pose an unnecessary risk to patients. Therefore, FDA recommends patients use valsartan-containing medicines made by other companies or consider other available treatment options for the patient's medical condition.
- If you have medication samples from these companies, quarantine the products and do not provide them to patients.

Consumers and health care professionals should report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (https://www.fda.gov/safety/medwatch/) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)

- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178

**7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity**

Go to Press Release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity)

**FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities**

**The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.**

- Combined headspace method (/media/117843/download): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- Combined direct injection method (/media/117807/download): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- Direct injection GC-MS method (/media/123409/download): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- Headspace GC-MS method (/media/124025/download): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- LC-HRMS method (/media/125478/download): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- RapidFire-MS/MS method (/media/125477/download): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published methods to detect NDMA and NDEA (https://www.edqm.eu/en/ad-hoc-

projects-omcl-network) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). FDA has not validated EDQM's methods.

## Resources for You

- Search ARBs Recalls List (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and)
- Recalls of ARBs including Valsartan, Losartan and Irbesartan (/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)
- Nitrosamine Impurities in Medications (/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)

# Exhibit 32

# N-Nitrosodimethylamine

## CASRN 62-75-9 | DTXSID7021029

- IRIS Summary (PDF) (11 pp, 105 K)

**Key IRIS Values** | Other EPA Information

# Noncancer Assessment

**Reference Dose for Oral Exposure (RfD) (PDF)** (11 pp, 105 K)
Not assessed under the IRIS Program. Last Updated:

**Reference Concentration for Inhalation Exposure (RfC) (PDF)**
(11 pp, 105 K)
Not assessed under the IRIS Program.

# Cancer Assessment

**Weight of Evidence for Cancer (PDF)** (11 pp, 105 K)
Last Updated: 01/31/1987

| WOE Characterization | Framework for WOE Characterization |
|---|---|
| B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals) | Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) |

**Basis:**

- Induction of tumors at multiple sites in both rodents and nonrodent mammals exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

**Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF)** (11 pp, 105 K)

**Oral Slope Factor:** $5.1 \times 10^{1}$ per mg/kg-day
**Drinking Water Unit Risk:** $1.4 \times 10^{-3}$ per µg/L
**Extrapolation Method:** Weibull, extra risk
**Tumor site(s):** Hepatic
**Tumor type(s):** Liver tumors (Peto et al., 1984)

**Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF)** (11 pp, 105 K)

**Inhalation Unit Risk:** $1.4 \times 10^{-2}$ per µg/m$^3$
**Extrapolation Method:** Weibull, extra risk
**Tumor site(s):** Hepatic
**Tumor type(s):** Liver tumors (Peto et al., 1984)

You will need Adobe Reader to view some of the files on this page. See EPA's PDF page to learn more.

Contact Us to ask a question, provide feedback or report a problem.

# Related Links

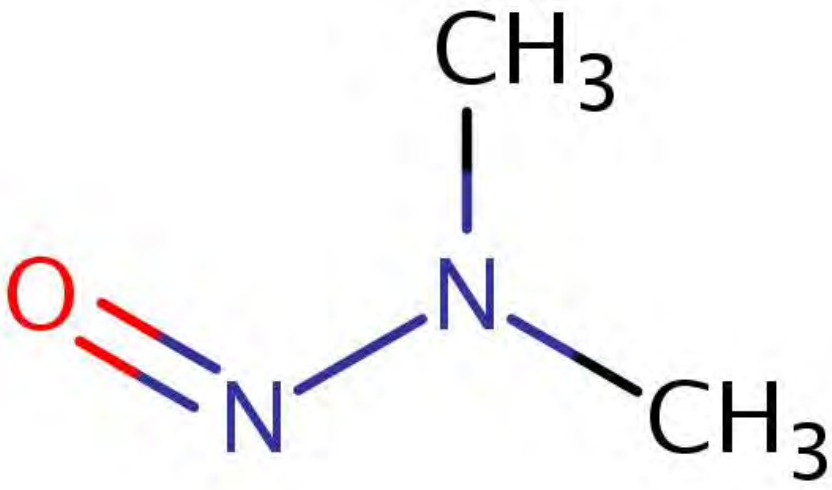
- EPA Chemicals Dashboard - N-Nitrosodimethylamine
- eChemPortal - Nitrosodimethylamine

# Tumor Sites

Hepatic

# Chemical Structure for

# N-Nitrosodimethylamine




## Synonyms

- Dimethylamine, n-nitroso
- Dimethylnitrosamin
- Dimethylnitrosamine
- Dmna: dmn
- Methylamine, n-nitrosodi-

more synonyms

LAST UPDATED ON {MONTH DAY, YYYY}

# Exhibit 33

# N-Nitrosodiethylamine

## CASRN 55-18-5 | DTXSID2021028

- IRIS Summary (PDF) (11 pp, 106 K)

**Key IRIS Values** | Other EPA Information

# Noncancer Assessment

**Reference Dose for Oral Exposure (RfD) (PDF)** (11 pp, 106 K)
Not assessed under the IRIS Program. Last Updated:

**Reference Concentration for Inhalation Exposure (RfC) (PDF)**
(11 pp, 106 K)
Not assessed under the IRIS Program.

# Cancer Assessment

**Weight of Evidence for Cancer (PDF)** (11 pp, 106 K)
Last Updated: 01/31/1987

| WOE Characterization | Framework for WOE Characterization |
|---|---|
| B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals) | Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) |

**Basis:**

- Induction of tumors at multiple sites in both rodent and nonrodent species exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

**Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF)** (11 pp, 106 K)

**Oral Slope Factor:** $1.5 \times 10^{2}$ per mg/kg-day
**Drinking Water Unit Risk:** $4.3 \times 10^{-3}$ per µg/L
**Extrapolation Method:** Weibull, extra risk
**Tumor site(s):** Hepatic
**Tumor type(s):** Liver tumors (Peto et al., 1984)

**Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF)** (11 pp, 106 K)

**Inhalation Unit Risk:** $4.3 \times 10^{-2}$ per µg/m$^3$
**Extrapolation Method:** Weibull, extra risk
**Tumor site(s):** Hepatic
**Tumor type(s):** Liver tumors (Peto et al., 1984)

You will need Adobe Reader to view some of the files on this page. See EPA's PDF page to learn more.

Contact Us to ask a question, provide feedback or report a problem.

# Related Links

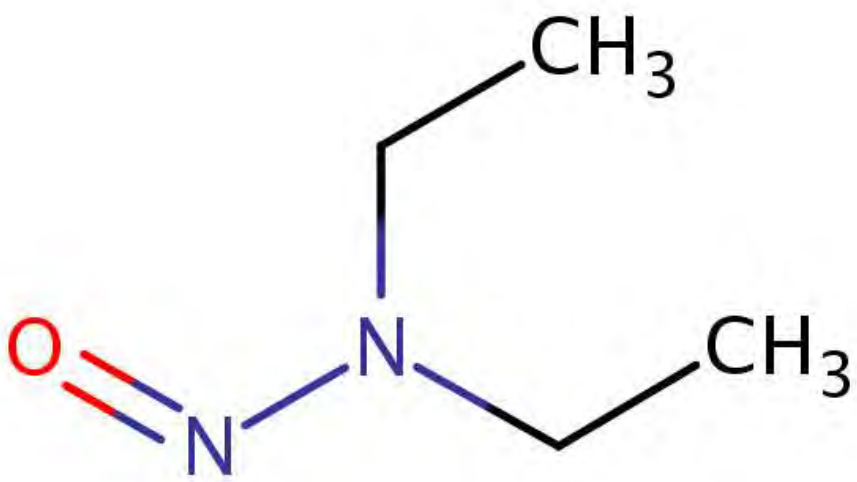
- EPA Chemicals Dashboard - N-Nitrosodiethylamine
- eChemPortal - Nitrosodiethylamine

# Tumor Sites

Hepatic

# Chemical Structure for

# N-Nitrosodiethylamine




## Synonyms

- Dana: den
- Dena
- Diaethylnitrosamin
- Diethylamine, n-nitroso
- Diethylnitrosamine

more synonyms

LAST UPDATED ON {MONTH DAY, YYYY}

# Exhibit 34

# Welcome


Empowering a healthy tomorrow

# SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

By: Edmond Biba
Senior Scientific Liaison,
Science – General Chapters

Webinar
July 28, 2020

# Background

## Introduction

- Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- However, their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens.
- They are part of a group of high potency mutagenic carcinogens referred to as the “cohort of concern” in ICH M7. This “cohort of concern comprises aflatoxin-like, N-nitroso- (functional group of nitrosamines), and alkyl-azoxy compounds

# Exhibit 38

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**
**CAMDEN VICINAGE**

| | |
|---|---|
| **IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION** | MDL No. 2875<br><br>Honorable Robert B. Kugler, District Court Judge |
| **This Document Relates to All Actions** | |

**STIPULATION OF ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.**

Pursuant to Special Master Report and Order No. 56, in exchange for Plaintiffs' agreement not to further examine a witness at deposition regarding the statements identified herein, Defendant Zhejiang Huahai Pharmaceutical Co., Ltd. ("ZHP") hereby stipulates as follows:

1. ZHP states that there are no health benefits associated with the presence of NDMA or NDEA in valsartan.
2. ZHP states that the publication *Purification of Laboratory Chemicals* (4th ed.) by W.L.F. Armarego and D.D. Perrin, which was first published in 1996 and documented scientific knowledge at that time, states on page 192 that DMF

"[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide."

3. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:
    a. ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.
    b. The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.
    c. Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.
    d. ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. ZHP is not saying that it was not possible to know that DMF could degrade.
    e. ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

4. With regard to the Change Request Form identified as Exhibit 195 to the March 28/29, 2021 deposition of Peng Dong (copy of Exhibit attached hereto as Exhibit 1), ZHP states the following:

   a. The "Explanation Section" in Section 2 of the Change Request form on the page bearing Bates number ZHP01843067 provides a summary of the explanation for why the process change from the triethylamine hydrochloride process to the zinc chloride process was undertaken.

   b. One of the reasons for the quality review described in Section 3 of the Change Request Form on the page bearing Bates number ZHP01843069 was to identify impurities due to the new process.

   c. Section 3 of the Change Request Form on the page bearing Bates number ZHP01843070 provided that if this change was against cGMP code, it was supposed to be rejected.

| | |
|---|---|
| Dated: May 13, 2022 | *<u>/s/ Richard T. Bernardo</u>*<br><br>Richard T. Bernardo<br>SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP<br>One Manhattan West<br>New York, NY 10001-8602<br>richard.bernardo@skadden.com<br><br>Jessica D. Miller<br>SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP<br>1440 New York Avenue, N.W.<br>Washington, D.C. 20005<br>jessica.miller@skadden.com<br><br>Counsel for Defendant |

# Exhibit 39

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

| | |
|---|---|
| IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION | MDL NO. 2875<br>CIVIL ACTION NO. 19-2875 (RBK/JS) |
| THIS DOCUMENT APPLIES TO ALL CASES | HONORABLE ROBERT B. KUGLER |

- CONFIDENTIAL INFORMATION -
SUBJECT TO PROTECTIVE ORDER

REMOTE VIDEOTAPED EXPERT DEPOSITION OF
FENGTIAN XUE, PHD
Friday, February 3, 2023
10:04 a.m. Eastern Time

Stenographically Reported by:
Denise Dobner Vickery, CRR, RMR,
Court Reporter, Notary Public JOB NO.: 329090

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Also Present Remotely Via Zoom:

JUDY DIAZ, Videographer
JESSICA DAVIDSON MILLER, ESQ., Skadden Arps
CHRISTOPHER HENRY, Mazie Slater



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DEPOSITION EXHIBITS

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P R O C E E D I N G S

- - -

THE VIDEOGRAPHER: We are now on the record.

My name is a Judy Diaz. I'm a legal videographer for Golkow Litigation Services. Today's date is February 3, 2023 and the time is 10:04 a.m.

This remote video deposition is being held in the matter of Valsartan, Losartan, and Irbesartan Products Liability Litigation MDL.

The deponent is Fengtian Xue, PhD.

All parties to this deposition are peering remotely and have agreed to the witness being sworn in remotely.

All counsel will be noted on the stenographic record.

The court reporter is Denise Vickery and will now swear in the witness.

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- - -

FENGTIAN XUE, PHD

called for examination, and, after having been duly sworn, was examined and testified as follows:

MR. BERNARDO: And I apologize for interrupting so quickly. I intended, Adam, to get this in before Jessica made a start.

I just want to point out, Adam, that Dr. Xue has been recovering from COVID all week and has been powering through and is here and ready to go, as he'll tell you.

I just want to ask for your patience because he may be soft-spoken at times, and I told him to try and speak up just because his voice is a little worn. And also we may have to ask for a break sooner than ordinarily, but I'm sure that won't present a problem.

I just wanted to explain to you the reason for all that.

MR. SLATER: Whatever it is,

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we're here for the duration. We are here.

- - -

EXAMINATION

- - -

BY MR. SLATER:

Q. Hope you feel better. Hope you are feeling better, Doctor.

A. Thank you.

Q. Let me -- by the way, to pronounce your name tell me, the proper pronunciation please.

A. Please call me Fengtian. Or you want me to --

MR. BERNARDO: I think he's asking for how to pronounce your last name, Doctor.

BY MR. SLATER:

Q. Yes, Doctor, because I've heard it pronounced a few different ways. I want to make sure I get it right.

A. What is the fast way "Xue."

Q. Xue. Okay. I think I can handle that.

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MR. SLATER: All right. Great. Are we on the record now?
THE VIDEOGRAPHER: Yes, we're on the record.
MR. SLATER: Okay. Great.
BY MR. SLATER:
Q. Good morning, Dr. Xue.
A. Good morning.
Q. I'm Adam Slater. We've just introduced ourselves.
You understand we're here to take your deposition, correct?
A. I understand.
Q. Have you ever had your deposition taken before?
A. First time in my life.
Q. There's a few important things that you should know.
The one that's most important to me is that if you don't understand a question or it doesn't make sense to you for any reason such that you don't know if you can answer it truthfully or accurately, just say something. You can say, "I don't understand your question." Maybe you don't

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hear it. Maybe I mispronounce a scientific term. It could be for a whole host of reasons that you don't feel comfortable you understand what I'm asking.
You can just tell me that. I might ask what's unclear. I might ask what the issue is. You can tell me, and I'll try to work to get a question out that you feel comfortable answering on the subject matter I'm trying to get into.
Okay?
A. Thank you.
I also want to point out, I'm -- I speak English for 20-plus years but still my vocabulary is not the biggest. Sometimes if you speak a word, I may not be able to recognize what the meaning of the word. I may also point that out.
Q. If for any reason you feel like you need clarification on anything I'm asking you, I want you to tell me.
A. Thank you. I will do.
Q. There may be objections during the course of the deposition. Lawyers are allowed to object. Mr. Bernardo can say, "Objection to the

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form of the question." What he's saying is, Mr. Slater, you're not answering the -- asking the question properly under the rules of evidence.
You may still answer the question. I would say in most cases you probably will. He's preserving his rights. I can re-ask the question differently. I can proceed with it. You shouldn't be thrown off by that.
Just let -- if somebody objects, just let us address it, and then I would think for most -- and you'll get into the rhythm -- in most cases you'll probably just answer the question, but it's allowed. The lawyer is allowed to object. So just don't -- it's not -- not something you have to be concerned about, but you'll hear the objections from time to time.
Okay?
A. Okay.
MR. SLATER: Let's first put up as Exhibit 1 the deposition notice. Actually, the responses and objections to the deposition notice. Let's do that.
(Document marked for identification as Xue Exhibit 1.)

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MR. SLATER: Yeah, I'm -- yeah, let's put it on the screen.
BY MR. SLATER:
Q. Dr. Xue, did you review the deposition notice that we had served in advance of the deposition?
A. Excuse me. Do I suppose to have this file also in the folder that sent to me?
Q. I don't know the answer to that question.
A. I just refreshed the folder that sent. Okay. Now I can see the file.
Q. Okay. I'm actually not asking about this document yet. It's just on the screen. I'm asking a different question.
A. Okay.
Q. Did you see the deposition notice that was served in this case for your deposition?
A. I am being seeing so many documents.
Q. On -- on the screen, we have Exhibit 1, which is "Defendants' Responses and Objections to Plaintiffs' Notice to Take Videotaped Deposition." This is for -- this is the response by the attorneys to our request for

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documents in advance of the deposition.
Have you seen this response?
A. I -- I think so. There's -- there's multiple items that I need to address there, right, to respond to those questions.
Q. Did you do that? Did you go through the various requests and -- and make sure that anything that was requested was provided to the attorneys to provide to us?
A. I think I did.
MR. SLATER: Okay. Great.
You can take that down.
Let's put up as Exhibit 2, the report, please.
(Document marked for identification as Xue Exhibit 2.)
BY MR. SLATER:
Q. We've put up on the screen Exhibit 2, which is the report we were served dated December 22, 2022, and it was signed by you at the end on page 58.
Is that the report that you wrote in this case?
A. Yes. You showed me the first page.

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By the first page, that is the report that I read.
Q. And attached to the report --
A. I'm sorry. I wrote, not read. I apologize.
Q. Okay. Attached to the report was a curriculum vitae.
Is that your up-to-date current curriculum vitae?
A. Can you explain what "curriculum vitae" mean?
Q. It's the list of your background, experience, your training, your education that we were provided.
A. Oh. Oh.
Q. It starts with your name at the top. It says that your title was associate professor, etc.
A. Yeah. Sorry. I used to call it CV. You know, as I said, the word was not sound directly to me.
Yes, I attach a copy of my CV to this report.
Q. And then listed as Exhibit A to the report was something titled "Materials Reviewed

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and Considered."
Was that a complete list of the materials that you reviewed and considered as of the time that you authored your report dated December 22, 2022?
A. Yes, I did all the -- my own search. Also the material provide by the counsels. I think everything that I considered when I write this report, offer my opinion, I put in that. I think it's called a list of material.
MR. SLATER: Chris, can you go to that Exhibit A, please, the first page? Perfect.
BY MR. SLATER:
Q. Looking at the Exhibit A to your report items 8, 9, and 10 are interviews with Min Li, Jucai Ge, and Jinsheng Lin.
Do you see that?
A. Yes, 8, 9, and 10 are the two -- sorry -- three interviews.
Q. Did you take notes of those interviews?
A. I didn't take notes for neither of them.

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Q. Was anybody present when you interviewed those three people?
A. Well, you mean besides me and the three people individual?
Q. Correct.
A. No, only a pair of us. Like if I interview Min Li, only Min Li and I was there.
Q. Were -- were these interviews conducted in person or by some other means?
A. All of them was through Internet.
Q. Were you able to see each other? Was it by Zoom or something similar to Zoom?
A. I didn't see them at all.
Q. Were the interviews spoken or were they e-mails back and forth?
A. I first reach out to them to make appointment. During the interview was just talk.
Q. Do you know where each of those people were located when you interviewed them?
A. Honestly, I don't know. I don't remember ask that question. I should not make speculation. I believe Jucai Ge and Dr. Jinsheng Lin was in China. Dr. Min Li might be in the U.S.
Q. Had you ever met any of those people

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before you interviewed them?
A. I never met either of the three.
Q. Were these interviews recorded?
A. No, I didn't record any of the interviews.
Q. When I went through your report, I did not see any reference to those interviews, any of the content of those interviews.
Am I correct that nowhere in your report did you actually recite what those people told you during the interviews?
A. Well, I talk them to them before I start writing my report. So some of the knowledge or information that I heard -- I heard from them I confirm with them my, you know, gave me idea that I -- that we think the conservation scope that I used to form my opinions.
Q. In forming your opinions in this case, did you rely in part on those interviews with Min Li, Jucai Ge, and Jinsheng Lin?
A. When you say "rely" means I cite them or I consider them. I just don't quite know what you really mean here.
Q. In terms of the basis for the

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opinions you gave in your report --
A. Right.
Q. -- was one of the things that you relied on the interviews with Min Li, Jucai Ge, and Jinsheng Lin?
MR. BERNARDO: Object to the form of the question. Vague.
BY MR. SLATER:
Q. I'll ask the question again.
In forming the opinions you formed in this case --
A. Right.
Q. -- was one of the things that you relied on the information you got from Min Li when you interviewed him?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: As I said just now, when I interview not just Min Li, each one of the three ZHP employees, I had a conversation and they gave an introduction about what happened. I usually ask a couple questions.
Yeah. They will highlight

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something that they want me to know. As I said, I -- I consider that those when I form my opinions.
BY MR. SLATER:
Q. Did you speak with anybody else from ZHP or any of the companies affiliated with ZHP other than Min Li, Jucai Ge, and Jinsheng Lin with regard to this matter?
A. With regard to this case, I never speak to anybody other than the three that listed here.
Q. Before you were retained in this case, did you know anybody that has worked at ZHP or Prinston?
A. No, I actually know nobody from those companies.
Q. Do you know a toxicologist named Charles Wong?
A. I have no idea because, you know, Charles Wong is a very common, you know, Chinese name.
Q. I'm asking about a toxicologist named Charles Wong.
A. No, I don't know any toxicologist

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named Charles Wong.
Q. Is there any place in the report where you actually refer to anything that Min Li, Jucai Ge, or Jinsheng Lin told you during those interviews?
I didn't see anything like that, but I'm asking if that's there and I missed it.
A. I didn't cite anything that either one of the three people -- Jinsheng Lin, Jucai Ge, or Min Li -- told me.
Q. There's a number of documents listed on this list of Materials Reviewed and Considered.
Did you read every single one of the documents listed?
A. I probably read every one. That's why it's listed here, but, you know, it has been a long journey. I've been reading so many documents, and also I did literature search on multiple reaction situations. I cannot say that I remember everything that I read and memorized because this report was written -- don't know -- 40 days ago. I honestly have been fairly busy and, on top of that, I've been suffer from COVID recently.

So I cannot say that I remember everything that I -- I saw, but I'll try my best.

Q. Are you alone in that room that you're in right now?

A. I am.

Q. Do you have any documents in hard copy with you for this deposition?

A. Well, I have this plain report of myself that you showing me in front of me. It's closed. I'm not sure whether I'm allowed to read it.

Q. Yes, you are.

A. Am I allowed to read my report?

Q. Yes.

A. Okay.

Q. I'm going to ask you at times about the report, or if I ask questions and you need to refer to the report, you can do so.

What I'm asking you right now is just what documents you have. If you can just list for me what you have out there.

A. That's the only -- only document I have, other than the two screens in front of me.

Q. And when you say "the two screens,"



one screen for the Zoom and then another screen where you can electronically access documents?

A. Yes. So I have the screen. I see you and I see everybody and see the document of Exhibit A. On the other one, I have the folder. It's called my name "Marked Exhibits" right now showing on there.

MR. SLATER: You could take that off the screen, Chris.

BY MR. SLATER:

Q. You said you have your report in front of you. So I'm not going to need to put the report up anymore. You can look at it.

Unless I need to show you a particular thing, I can put it up, but it will just be easier. You can look at it.

A. Yes, that's --

Q. You can look at something.

Your report sets forth various opinions.

Are those all of the opinions that you formed in this case at the time you wrote the report?

A. So you talk about the three reports



-- sorry -- three opinions on page 3?

Q. Those are your three opinions in this case, the three bullet pointed opinions on page 3?

A. Yes.

Q. You also wrote a supplemental report.

MR. SLATER: Why don't we throw that up, Chris, just to get it identified.

Yeah, let's do as Exhibit 3 the supplemental report.

(Document marked for identification as Xue Exhibit 3.)

BY MR. SLATER:

Q. Unless, Doctor, do you have that handy also or do you only have your --

A. No. I didn't even know I'm allowed to use the report. So I didn't print out the supplementary. Maybe I have to --

Q. No problem.

A. -- put it up when I need it. Thank you.

Q. Do you recognize Exhibit 3 as the



supplemental report you wrote in this case dated January 30, 2023?

A. Yes.

Q. It looked like this was a response or a commentary on some of the testimony that was given by Dr. Najafi in his deposition; is that correct?

A. Yes, it is correct.

Q. Did you form any new opinions and place those in that report, or did your opinions as stated on page 3 of your first report remain the same and did they remain as your only opinions?

MR. BERNARDO: Object to the form of the question. Vague.

BY MR. SLATER:

Q. I'll ask the question again.

Did you add any new opinions when you wrote the supplemental report?

I didn't see any new opinions, but I just want to make sure from your perspective you didn't add any new opinions when you wrote the supplemental report.

A. As he point out -- sorry.

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MR. BERNARDO: I was just going to object to the form of the question.

But you can go on, Dr. Xue.

THE WITNESS: As you point out, this report was written recently to address Dr. Najafi's deposition recent happened. I'm trying to use my knowledge in chemistry to address some of his statements.

My main opinions are listed in my earlier report, the main report, the three points stays.

BY MR. SLATER:

Q. The three opinions set forth in your initial report remain the same even when you wrote the supplemental report.

Is that what you're telling me?

I just want to confirm that.

A. (Reviews document.)

Q. Let me ask the question differently.

A. I'm sorry. Yes, go ahead.

MR. BERNARDO: I think he's just looking to confirm, Adam, just give

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him a moment.

BY MR. SLATER:

Q. Yeah.

A. Yeah, I just want to make sure everything I said is -- is --

Q. Oh, I didn't realize you were looking at the report to answer the question.

Go ahead. I'm sorry. Go ahead.

A. Yeah.

Q. And just for the record, the question is: The supplemental report did not change or add any new opinions; is that correct?

A. I'll agree there's no additional point that I want to add. I just want to address the -- the comments or points that Dr. Najafi raised during his deposition recently.

MR. SLATER: And just to be fair, with regard to the reliance list, let's mark as Exhibit 4 the "Amended and Supplemental List of Materials Reviewed and Considered."

(Document marked for identification as Xue Exhibit 4.)

BY MR. SLATER:

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Q. We'll mark this as Exhibit 4.

I saw that some depositions were added to the list of Dr. Hecht and Dr. Najafi and Dr. Plunkett.

To your knowledge, was anything else added to this amended and supplemental list as compared to the original list?

A. I add because these, you said those three depositions happened after my original report, and I reviewed them. So I want to add these depositions to the material conservation.

Also, I also add a paper that was -- it's just one paper I want to add to that as well.

Q. Which paper was that?

A. I honestly don't remember exactly what the paper's title was, but it -- yeah, I can look through to -- to find it. Is that --

Q. Do you recall why you wanted to add that paper? What the subject matter was?

A. Well, because that's just when I -- when I originally write the report. There's a bunch of examples of reaction conditions I want to support. So I did literature search. I found these maybe -- I don't know -- few dozens of

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papers and those are one of that.

And I honestly don't remember what was the reason, but I just put on -- I run literature and I recognize later on, and then I decide to just give the counsel that additional paper.

Q. We also received an e-mail yesterday, February 2nd, that indicated that when you were preparing for this deposition, you noticed that a few of the deposition transcripts you reviewed were inadvertently omitted from the list of materials considered, including Jucai Ge deposition May 26 and May 27, 2022 and Pang Dong deposition April 1, 2021.

Is that correct that you also had read those depositions?

A. Oh, I did.

Q. Did you read the deposition transcripts complete from cover to cover?

A. I honestly won't say that. Because especially Jucai Ge's it's very long. I won't say I read line to line every line, but I cover most of part when I prepared for my -- for my report.

For -- for Dong -- I forgot his

first name -- that deposition I only read a small portion. Because that I remember was I asked for this deposition because Dr. Najafi or maybe Dr. Hecht -- I forgot -- during their deposition, they use this as their additional, one of the papers, 2010, some -- some therapeutic studies -- sorry -- theoretical calculations where that paper came to me as part of Pang Dong's deposition, and that's why I ask for the counsel to sent me his deposition to look.

But I didn't look Pang Dong's for the most part.

MR. SLATER: We can take down that reliance list.

BY MR. SLATER:

Q. I want to ask you a couple questions about your report again, the initial report, December 22, 2022, Exhibit 2.

A. Yes.

Q. The report lists a lot of facts, some in great detail, a lot of information.

Would that be information that you felt was most important to you in forming your opinions in this case? Is that why that



information is what you actually discussed in the report?

A. When I write report or any art -- scientific papers I wrote in my career, I always trying to present my opinion or my discovery in a way that I highlighting the case. I use some avenues to support my -- my -- my point. If I have opinion overall in scientific writing we call it conclusions, I usually also highlight that in the writing. So that's just my style.

I -- I guess I hope that answer your question.

Q. My question is: The facts that you discussed in your report.

A. Right.

Q. Are those the facts that were most important to you in forming your opinions?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: Well, I can only say that these are the fact that I, you know, I read. When I write this report, I mostly read the plaintiffs' experts' report from, I think, four experts, and



then I see their points and then I try to address their points in a way that my understanding of the science behind the case. Like the nitrosamines, NDMAs, NDEAs, these process. That's what I -- what I did.

I cannot really see that I highlight everything. Mostly we need to focus on what the experts on the plaintiff side talked about.

BY MR. SLATER:

Q. You prepared for this deposition, right?

Did you prepare for this deposition? Did you prepare yourself?

A. I did. You see what (indicates).

Q. Okay. Is one of the things you did in preparing for the deposition reading your report?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: Well, I don't --

BY MR. SLATER:

Q. Dr. Xue, it's a very simple



question.

A. I know.

Q. Did you read your report as part of your preparation for today's deposition?

MR. BERNARDO: Object to the form of the question. Argumentative.

Go on, Dr. Xue.

THE WITNESS: I wrote my report. I read my report.

BY MR. SLATER:

Q. So the answer is yes?

MR. BERNARDO: Object to the form of the question. Vague.

Adam, why don't you ask him the question. From what he demonstrated with his attire, I think it's clear he didn't understand what you meant by prepared.

He's trying to be very responsive as I can tell, but I think he pointed out at the very beginning of this deposition some language issues. So if you could just re-ask the question, I think he didn't understand it.

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MR. SLATER: Okay.
BY MR. SLATER:
Q. Dr. Xue.
A. Yes.
Q. Did you review documents, including your report, in order to prepare yourself to answer questions today during the deposition?
A. Oh, yeah, I did read my report.
Q. That's all I asked.
A. Okay. Thank you. I -- yeah.
Q. When you read the report in preparation for the deposition, did you think to yourself that there were any important facts that you're relying on that were not discussed in the report?
A. I read my report. I honestly never ask myself that question. I review all my core key opinions stay because I -- this is not something come to me simply, right? So I know this is important case. I did my study. I formed them, these -- these -- these opinions.
Yeah. I definitely read my report before the deposition, but I -- I don't think I, you know, I will question myself. This is

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something I seriously prepared.
Q. Are there any facts that are important to you that you're relying on to support the opinions you gave that are not in your report, that are not discussed in the report? Anything you can point to?
The answer may be nothing. I just want to know if there's anything outside the report factually that you're relying on that's not discussed in the report that you can tell me right now.
It's a yes-or-no question.
A. Can I get a confirmation? Are you asking whether every single point that I rely on to form this report is covered or listed in my report? Is that your question?
Q. My question is: Are there any facts that are important to you in forming your opinions?
A. Right.
Q. Facts that you're relying on to say, "This is my opinion. It's based on this." Where you would say, "I didn't talk about that fact in my report."

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Is there anything like that?
MR. BERNARDO: Object to the form of the question. Vague. Broad.
THE WITNESS: I honestly -- I cannot answer this question with a yes or no. Because, you know, writing papers or writing reports is, it's everything come to me. I read. I digest the opinions from the experts on -- on the plaintiff side. Excuse me.
And then I do my own little search. I digest the case. Understand each piece, what the science told me, and then I form my own.
Like as you just read, there are three key things. I don't know whether I can say every single fact was addressed or shown in the -- in my report. Yeah.
I hope that answer your question.
BY MR. SLATER:
Q. When I read your report, both your reports, I did not see any criticisms by you of

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ZHP.
Are there any opinions that you have in any of your reports where you criticize anything ZHP did?
A. Well, I -- I just -- I think I explain this just now, right? So I --
Q. It's a yes-or-no question, Doctor. Let me ask it again because I think you're -- I don't know what you're -- you may not have been deposed before, but if you're going to give me long stories in response to questions that are simple yes or noes, we're going to go much longer than necessary.
So let me try it again with you.
MR. BERNARDO: Objection.
BY MR. SLATER:
Q. Make it a smaller question for you.
Are there any criticisms of ZHP in either of your reports?
A. I really tried my best to help. I'm not trying to not answer short, right? But these questions are not to me yes or no questions.
Q. All right. Well, then, let me ask it again so that I try to get it to a yes or no.

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Do you have any opinions critical of ZHP where you're saying ZHP did something wrong or failed to do something it should have done?

A. I'm -- I was retained by the ZHP counsel to offer my opinion to address the plaintiffs' experts' point and since during I read all these report from the plaintiffs' experts. They were saying everything ZHP did was wrong, right? So I was trying to address that.

So I really don't feel that I -- I have any, you know, when I approach this, come up with the report, I don't have any intention to do so.

Q. No intention to criticize ZHP in any way? Is that what you mean when you said -- listen, let me ask it again.

When you said, "I had no intention to do so," did you -- were you saying you had no intention to criticize ZHP? Is that what you meant when you said "to do so," yes or no?

A. Well, I probably didn't make myself clear. If that's my language issue, I already said I feel sorry about that. But I tried to explain, right?

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So I'm here as a -- as an expert in organic chemistry trying to address the experts on the plaintiff side points and then that's how, you know, I form my report around that theme.

So I'm -- in other words, I'm really -- I don't -- I'm not here to criticize anybody. I just want to address the point that the plaintiffs' expert offered.

I hope that answer your question.

Q. It does and it's helpful because it was something I was going to get into in a few minutes. So you brought me there so we can go there now.

I think what you're -- what you're telling me is that you -- rephrase.

I think what you're telling me is you understood your role in this case to respond to the plaintiff expert reports in the field of organic chemistry; is that correct?

A. I disagree.

Q. Okay. Let me ask a different question then.

What is your understanding of what your role was as an expert in this case?

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You just told me you were responding to the plaintiffs' experts.

Was there anything else that you thought was your role in this case?

A. My role is, I was retained by the ZHP counsel as an expert in organic chemistry to offer my own opinion about this whole case, and I was also given or, you know, provided the material, including the major material was the four report from the plaintiffs' experts. Of course, they have a lot of citation in there as well.

Yeah. So that's the scope of my -- my role here I thought because I'm an organic chemist. I might offer some expertise in my area. I try to understand the whole case throughout reading all the -- all the informations available to me, and I did my own search as well to see what the science was about at that time when they actually developed these processes, all these things. And then I come up with a report.

That's my understanding about -- sorry -- my role here.

Q. Did you form any opinions during

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your work as an expert in this case where the opinion is that ZHP either did something that it should not have done or failed to do something that it should have done?

A. Well --

Q. Actually, let me ask the question differently.

As you sit here now --

A. Right.

Q. -- as an expert, do you have any criticisms of ZHP?

MR. BERNARDO: Object to the form of the question. Asked and answered.

BY MR. SLATER:

Q. You can answer, Doctor.

Do you have any opinions critical of ZHP?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: I really don't want to repeat myself but --

BY MR. SLATER:

Q. It's a yes-or-no question, Doctor.

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A. As I said, I really tried if I can answer yes or no, that would be easy. I really cannot because this is, like I mention that I was retained as organic chemist to offer my opinion about the case. I offered all these effort report from the experts from the plaintiff side. I read them. I digest them. I do my own search.
Yeah. So I -- these three, as you just read the three, are my -- my -- my opinions. That's -- that I think is clear.
Q. Yeah. I'm asking you now.
A. Okay.
Q. As you sit here now.
A. Right.
Q. Do you have the opinion that ZHP did anything wrong?
A. Okay. So --
MR. BERNARDO: Wait. Wait. Object to the form of the question. And, Adam, he's trying to respond. I think the scope of his opinions are clearly delineated. He's trying to explain that in his report.
He's here to offer an opinion

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about organic chemistry, not company conduct. He's tried to answer your question. This sort of goes back to the hearing I recall with Judge Vanaskie saying, you know, you can ask it several times and then move on. So I object --
MR. SLATER: Rich. Rich.
MR. BERNARDO: I object --
MR. SLATER: Don't talk with me right now, please. That's -- you're totally out of line.
MR. BERNARDO: I object to this continued line of questions. Go on.
MR. SLATER: That's okay. I have a witness who's having a hard time even understanding or responding to my questions, and you're giving me a hard time about following up?
MR. BERNARDO: I think the witness --
MR. SLATER: I'm taking the deposition now, okay? If you want to put it in that context, then we'll -- then we'll get much more direct.

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BY MR. SLATER:
Q. Doctor --
MR. BERNARDO: I'm simply preserving my objection.
MR. SLATER: That's okay. I'm going to ask a question.
BY MR. SLATER:
Q. Doctor, as an expert in this case, did you consider whether or not ZHP failed to do anything in connection with the development of the manufacturing processes at issue in this case?
Did you think --
MR. BERNARDO: Object.
BY MR. SLATER:
Q. -- about that whether or not ZHP failed to do anything it should have done?
MR. BERNARDO: Object to the form of the question. Vague. Overly broad. Asked and answered.
You can answer, Dr. Xue.
BY MR. SLATER:
Q. All right. You can answer.
A. I'll try one last time. I really --
Q. It's a yes-or-no question, Doctor.

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MR. BERNARDO: Adam, please don't interrupt him --
THE WITNESS: As I said --
MR. BERNARDO: -- with saying it's a yes-or-no question. It is not a yes-or-no question, and he's trying to say that. Judge Vanaskie has already --
MR. SLATER: That's great. You're obstructing this deposition very early on. I don't appreciate it.
MR. BERNARDO: I disagree.
MR. SLATER: And please don't threaten me with court action.
MR. BERNARDO: I didn't threaten you with court action.
MR. SLATER: You did. You did.
MR. BERNARDO: I'm just observing --
MR. SLATER: You're wasting time on my record right now.
MR. BERNARDO: Adam, I think you're wasting time now.
BY MR. SLATER:

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Q. Answer the question.
Doctor, a new question.
As part of your review of this case, did you consider whether ZHP failed to do anything from an organic chemistry perspective that it should have done?
MR. BERNARDO: Object to the form of the question. Vague. Overly broad. Asked and answered.
Go ahead, Dr. Xue.
THE WITNESS: As I said, I really cannot say yes or no for this question.
I'm an organic chemist. I -- I review what ZHP did. They did the planning. They did the risk assessment. They did the testings. And I also, of course, read all the report from the plaintiff side about these issues.
And then I went out myself. As I pointed again and again, I'm a chemist. I went out to just search for the chemistry, what I rely on, what I steps myself, and what I'm here for.

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So I read all these things. That form the three points. I mean, for -- for -- for ZHP, they did what they can at the time the knowledge available to them.
I hope -- I really hope that answer your question.
BY MR. SLATER:
Q. I read your report. I saw no --
A. Excuse me.
Q. Okay. I'll start over.
I saw your report. I saw no opinions critical of ZHP in your reports.
Were there any opinions in your reports critical of ZHP?
MR. BERNARDO: Object to the form of the question. Asked and answered.
You can go ahead, Dr. Xue.
THE WITNESS: Are you asking in my -- my report I'm facing now is there any opinion criticizing ZHP?
BY MR. SLATER:
Q. That's my question.

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A. I have this report. I think the opinions are there, right? So there that the three bullets that we read upfront was my opinion.
Q. So the answer is, no, you have no opinions in your report critical of ZHP; is that correct?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: Well -- well, I think we are -- we are making circles here, right? So we talk about this for I don't know how long, but this -- I describe my view of my role here. I stick with that.
I tried to be an expert to do my job and tried to offer my opinion based on my search, my understanding of the case.
BY MR. SLATER:
Q. Doctor, do you know what you wrote in your report?
A. I do. I wrote the report myself.
Q. Right.
Are there any opinions in your

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report critical of ZHP?
It's a yes-or-no question. I didn't see any. I just want to confirm I didn't miss it.
MR. BERNARDO: Object to the form of the question.
THE WITNESS: Well, I'll try one more time.
I offered my opinion based on what I search, what I learned, what I read, and what I believe.
BY MR. SLATER:
Q. I did not see any opinions in your report criticizing ZHP.
Am I correct that there are no opinions you wrote in the report where you criticized ZHP?
MR. BERNARDO: Object to the form of the question. Asked and answered.
Go ahead, Dr. Xue.
THE WITNESS: I have the three opinions, right, out there. ZHP, they did what they can, right? They don't have -- based on what they have

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specifically at the time when all these processes they developing. That's what available to them. So that's what -- what I form opinion.

I'm not -- sometimes those -- a lot of things it's not like absolute, right? So, yes, it must be like this. It must be like that, right?

So I have to judge based on my own expertise, based on what other people talk, and what I learn from the science to come up with a reasonable, appropriate judgment of myself.

I really think that that -- that that's what I do here.

BY MR. SLATER:

Q. Did you read the deviation investigation reports written by ZHP?

A. Well, I -- I read you know, right? So this is big case. I read so many documents.

Q. Doctor, do you know what the deviation investigation reports are? Do you know what those documents are?

A. I think those are -- if you -- do

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you have the document? Can we see the document together?

Q. Sure.

MR. SLATER: Let's put up the one that we've been talking about that we were talking about before. I guess it was Exhibit 210. The E318003 version 2. Put that on the screen.

THE WITNESS: Will that be Exhibit Number 5?

MR. SLATER: That will be Exhibit Number 5.

(Document marked for identification as Xue Exhibit 5.)

BY MR. SLATER:

Q. For the record, he's uploading -- we're uploading as Exhibit --

For the record, we've uploaded Exhibit 5, which is the November 5, 2018 deviation investigation report titled "Investigation regarding unknown impurity" and then in parentheses "(genotoxic impurity) of Valsartan API (TEA process)."

Do you have that? Do you see it?

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MR. SLATER: You can put it on the screen.

THE WITNESS: I just got it loaded on my screen.

As I said, I read so many things. This looks --

BY MR. SLATER:

Q. Doctor, I'm not asking you about all the things you read.

I'm literally asking you: Have you read this document?

A. I saw this document before, but as I said, if you want me -- ask me about details in here, I need to kind of -- you need to direct me there so I cite. I don't know. This --

Q. Doctor.

A. This is 300 pages.

Q. Dr. Xue, we're going to do much better today if you answer the questions I'm answering and then don't go and tell me something else. Like I wasn't asking you about whether I'm going to ask you questions.

I asked you one question. The question is: Did you see this deviation

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investigation report?

A. I do.

Q. Yes or no?

A. I do.

MR. BERNARDO: Object to the form of the question.

BY MR. SLATER:

Q. Did you consider this report in forming your opinions in this case?

A. So all the document that's made available, I read them and then I judge, and then I decide to form my report. So in that case, yes, I did consider everything including this particular one to form my opinion.

Q. As you sit here now, have you formed any opinions -- well, rephrase.

As you sit here now, do you have any disagreement with any of the conclusions that ZHP formed and documented in this deviation investigation report?

MR. BERNARDO: Object to the form of the question. Vague. Overly broad. Goes beyond the scope of his disclosure as an expert.

Go ahead, Dr. Xue.
MR. SLATER: Let's keep our objections to good-faith objections, too.
MR. BERNARDO: You have to explain to me what remotely was in bad faith about an objection that, pursuant to Judge Vanaskie's instruction, gives you as simply as possible some understanding. That was as cryptic as I can be, Adam.
MR. SLATER: Okay.
THE WITNESS: Well --
BY MR. SLATER:
Q. Answer the question, Doctor.
A. I will try to answer. Can you -- the question is kind of long. Can you chop it into small pieces so I can handle?
Q. Okay. Do you know what a deviation investigation report is? Do you know what this document is?
A. Yes. This document was actually in 2018 in July. That's after the nitrosamine was already known to be in some of the batches of the valsartan API, and then they did -- I think this



is like a retrospectic or backward study. That's my understanding about this.
Q. Did you see that during the course of this report ZHP drew certain conclusions and made certain findings? Did you -- did you notice that when you read the report?
MR. BERNARDO: Object to the form of the question. Overly broad.
THE WITNESS: Right. As I said, this is like -- although you don't like my comments, but this is 300 pages. I honestly I don't have a super good memory about everything I read.
If you can, please, if you can point to the section that you want me to address. Because I honestly I can't really just off my head to say everything or memorize everything you talk about here.
I -- I really try my best tried to help everybody here.
BY MR. SLATER:
Q. It's not -- with all due respect, I don't need help. What I need is answers to my



questions. So that's what I need.
So I'm going to ask you this.
I read your report. I did not see anywhere in your report where you said that any conclusion or finding by ZHP in its deviation investigation reports that you disagree with any of those conclusions or findings.
Do you disagree with any of ZHP's conclusions or findings that were placed in their deviation investigation report?
MR. BERNARDO: Object to the form of the question. Beyond the scope of his disclosure. Overly broad.
Go ahead, Dr. Xue.
THE WITNESS: Well, if you can show me.
BY MR. SLATER:
Q. No, I'm not. Doctor, let's stop right there. I'm not going to show you.
MR. BERNARDO: No, no, no. Let's stop interrupting the witness, who's simply asking if you could show him something to refresh his recollection, he'll answer. Okay? So let's stop the



interrupting each other.
THE WITNESS: I'm --
BY MR. SLATER:
Q. That's not the question, though. So that's --
A. I'm here --
Q. I withdraw the question, Doctor, because we're -- we're honestly at some point I'm going to stop the deposition if I cannot get intelligible answers to questions, and I'm just going to send the transcript to the court and say that counsel needs to reprep their witness to be able to actually answer a question with a direct answer.
It's not the ground we covered.
MR. BERNARDO: Now I object. That's a threat. That's --
MR. SLATER: No. I'm feeling very frustrated because I cannot get an answer to a question.
BY MR. SLATER:
Q. And so here's the question, Doctor.
A. Yes.
Q. If you disagreed with any of Z --

well, let me ask the question differently.
As a general matter, you understand that in the deviation investigation report, ZHP analyzed why the NDMA and NDEA contamination occurred in its valsartan API.
Do you understand generally that was the purpose of this document?
A. That -- that's something. At least to my understand, that's something included in this study.
Q. Okay. Do you disagree with any of the findings or conclusions by ZHP that they documented in analyzing what happened?
MR. BERNARDO: Objection.
THE WITNESS: Well, here's --
MR. BERNARDO: Wait a minute, Doctor.
Object to the form of the question. Vague. Overly broad. Beyond the scope of his disclosure.
Go ahead, Dr. Xue.
THE WITNESS: Well, as I said, right? So if you ask me whether I disagree with some conclusion, I think I



have at least the right to know what conclusion you talk about here, right?
So also these regulatory work is really -- we are moving kind of outside of my -- my expertise.
I try to do everything that I can to offer in my -- in my area, but if you don't even show me what -- what conclusion you are talking about here and -- and what at least really chemistry related or -- or it's not even my area.
I just don't want to get anywhere that is -- is not my expertise. I'm sorry.
BY MR. SLATER:
Q. Okay. I read your report very carefully, Doctor. I did not see any opinions in your report where you said that ZHP made a finding in a deviation investigation report that you disagree with.
There's no such opinion in your report, right?
A. Well, because what we -- I think we kind of moving back to the last question.



I'm here as a chemist addressing the experts' opinions from the plaintiff side. If they raise anything, I try to address. I read the whole thing. I, you know, I tried to look for my scientific basis to address those.
I don't know why you think -- or maybe I'm wrong -- I should actually be responsible also for finding any evidence to prove that ZHP did anything wrong.
Q. Doctor, I'm not trying to evaluate anything other than to confirm that I didn't see a particular opinion in your report.
So all I'm asking you is this.
You wrote a report dated December 22, 2022.
A. Right.
Q. I don't see any opinion in that report, which is 58 pages long, where you said that ZHP made a finding or drew a conclusion in a deviation investigation report that you disagree with.
I just want to make sure that you can confirm for me, "Yes, you're right, Mr. Slater, I didn't form such an opinion and put



it in my report." That's all I'm asking.
Am I right?
MR. BERNARDO: Dr. Xue, he's simply asking to confirm that what he said is not written in your report. Just --
THE WITNESS: Right.
I think I answered that because I have the three, three bullets, three opinions I wrote clearly. Beyond that, that's not my key opinions. I -- yeah. So that means I don't have those opinions. The three key opinions I listed clearly in my report already.
That make sense to you?
BY MR. SLATER:
Q. You're holding yourself out as an expert in this case as an expert in the field of organic chemistry; is that correct?
A. Yes.
Q. Do you hold yourself out as an expert with regard to the FDA?
A. Can you clarify what "FDA" mean here?

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Q. Are you holding yourself out as an expert with regard to the FDA's oversight of the API manufacturing process for drugs like valsartan?
A. Can you also explain to me what "oversight" mean?
Q. You don't know what "FDA oversight" means?
A. I see oversight as like -- like supervise, oversee. So but specifically, what do you mean by "oversight"? Are you talking about FDA regulations?
Q. I will ask it differently.
Are you holding yourself out as an expert with regard to FDA regulation of the development and manufacture of drug products?
A. On the regulation part, as I made it clear, I'm not expert at all in regulatory science.
But in term of drug development or -- or those technical processes involving organic chemistry, because the nature of my own research and training, I have those background.
Q. The part you just told me about at

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the end of your answer is not what I asked you about.
I asked about the FDA regulation of drug development and drug manufacturing.
You're not an expert in that area, correct?
A. Well, if that's, again, my language apologize, but I think your question was not quite what you are saying, right?
So you are saying I judge myself as the expert in manufacturing, development. All these are not just regulatory. These are -- these are matching my field, right? These are reaction involved, the chemistry involved and then you have, you know, there are all these judgment, all these assessment or testing, those are there, right?
So, but if you talk about regulation like what is required? What -- what -- what is GMP? What -- what are those, you know, for different things, APIs, what the standard of this? That's where I am not.
I want to make it clear. This is not -- I thought just now I was trying to answer

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your question, not trying to cut you adding additional useless information there. I'm really trying to help.
Q. You're not holding yourself out as an expert with regard to Good Manufacturing Practices, correct?
A. I know GMP, but I'm -- I'm here, as I said upfront, I'm an organic chemist. I'm here for that, but I know GMP, but I'm not an expert in those regulations so those -- those -- those rules of things.
Q. From reading your CV, it's my understanding that you do -- well, actually, why don't you tell me in a simple short version what it is that you do professionally.
A. I'm an associate professor. I do therapeutic development. I own a lab. We -- we -- we -- what we work on multiple projects try to develop different drugs for different type of human diseases.
Q. And I saw a term small molecule -- "small molecule therapeutics"?
A. Yes.
Q. What does that mean?

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A. Thank you for reading my CV.
Q. What are small -- rephrase.
I saw in your CV the term "small molecule --
A. Yeah.
Q. -- therapeutics." What does that mean?
A. Small molecule like, for instance, we all know valsartan is a small molecule. So therapeutics means drugs. Like valsartan, you know, is a -- is a small molecule drug. So that's what I do.
Q. You develop the -- the molecules that actually are going to have an impact physiologically on a person's body to address a disease basically?
A. That's our goal. We haven't really got anything on the market yet.
Q. Are you involved in the development of a drug product for manufacture and sale on a commercial basis? Meaning after you develop or work on developing the molecule, are you then involved in if a pharmaceutical company -- well, let me ask the question differently.

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Do you have any experience working with the actual development of a manufacturing process for large-scale manufacturing of a drug product for commercial sale? Is that something that you've done?

A. Well, for marketing, put things advertisement or setting or, you know, all these, I have no clue. I have never done those.

But for development, right? So for just point out the FDA purpose, I never really involved in the regulations or registers, all these thing. Although we try and move there.

So, but what we do here is a lot of research. It's close to identification, synthesis, development, characterization of the compound and, of course, we do animal variation, big or small animals. So the goal is to put things on market.

So I don't know whether that answer your question.

So a lot of my thing, my -- my -- my research scope is -- is stopped before like packaging, dosing or -- or advertisement.

I don't know whether that answer

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your question.

Q. Well, let me give you -- try to do it with using some of the terms from this case.

One of the manufacturing processes at issue in this case we've referred to as the zinc chloride process, correct?

A. Oh, yes.

Q. Okay. In your work, have you been involved in developing a drug -- drug manufacturing process such as like the zinc chloride process?

Meaning the drug manufacturing at a pharmaceutical company where they're actually going to manufacture the pills from the API, etc., that's not something you do, right?

A. Well, what you just described is a little broad. Like as I said, right? So we don't do manufacture in term of get to the dose like you got really commercial boxes to the patient. We don't do that.

However, my research or my work is a lot of development, just like the -- the reaction. I mean, we have to evaluate reaction. We have to read. Everyday everybody in my lab has to have

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their project cross.

Just like zinc chloride like you use as example. We don't do zinc chloride. We don't do valsartan at all in our lab. But we -- everybody has -- has some sort of project.

They all trying to make the compound in the efficiency that they want, and then they try to get the compound characterized in the high quality as much as we want. And then they want to make sure they can finish the project in a time efficient way means they don't want to get caught in trouble because they didn't plan well.

So all these are I think it's -- I personally have never worked for any pharmaceutical company in my career, but our lab, the nature of the research -- I won't -- I won't say. Maybe it's not the good analogy, but it's like a mini pharmaceutical industry here ongoing in my lab.

Q. Have you ever developed an API for commercial manufacture?

A. You're asking whether I have developed, right? So as I said, that's my goal, right? So to, you know, to get a drug on market

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to help people with their health. I haven't had any drug named after me at this moment.

Q. Have you ever been involved in the development of a manufacturing process for an API for a pharmaceutical company to actually manufacture the API? Has that something -- is that something you've ever done?

A. So you asking whether I'm involved in partnership with a -- with a pharmaceutical company?

Q. In any capacity.

Have you ever done that?

A. So we have collaborative projects sometimes with companies. I don't know whether that -- that qualified or that's what you were asking. But we -- as I said, we -- our research nature is very close to pharmaceutical company does. We don't worry about the product, you know, formulations or dosing or advertisement or selling. We don't. We never get in touch of that, but everything else actually we do.

Q. Let's talk about valsartan and try to talk in that context.

A. Sure.

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Q. What you do is you try to develop -- if we use -- if we used valsartan -- let me ask it differently.

What you do is you try -- you're the person who develops the valsartan molecule to treat high blood pressure.

That's -- that's what you do basically, right?

I know you didn't develop valsartan, but by analogy, that's what your research is to develop the actual -- the actual drug that's going to actually -- the molecule, the valsartan molecule.

That's basically what you'd be developing, right?

A. That's not quite the same.

See, what we do is we have a variation this compound. Let's see valsartan. As you said, we don't do valsartan in the lab. I just want to make it clear.

Valsartan is my target now. We need to figure out how to make valsartan in the lab in an efficient way because PhD thesis probably depends on the time. So they need to be very

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carefully work with me, design a synthetic route, and that would be used by the PhD student to get the valsartan synthesized.

And then we want to make sure we have good quality control of the valsartan product that we got is in good shape. So that means you can actually use that through all these testing.

And then we will -- we will -- we will validate valsartan does control the blood pressure in different models, in vitro, in vivo. And then we will -- we will say, hey, FDA, we have something. Please give us, you know, drug approval. But that -- we never touch that yet. That's the goal.

Q. Your focus is on developing the structure of the drug to treat the medical condition. That's what your research and that's what your work is focused on.

Do I understand that?

A. Well, I think you -- your -- your point is close, but not quite complete. Because my work, yes, is very, very critical for my -- my people to actually get the structure.

Like valsartan, you can imagine it's

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coming from something, right? So you're going to have some design strategy there to come with a structure. However, this is like a first sector, first stage.

Then the next stage is also super important is to make sure you produce in a timely fashion and a quality fashion a nice molecule. So you can use that for all the testing, PKs, PDs animal studies, toxicologies. All these things we do, that depends on the -- on the second sector the synthesis.

So we have three sectors. Just now you're saying I try to identify the structure. That's absolutely a very, very important sector, but it's not complete.

Q. Have you ever had input into the development of a manufacturing process for an API?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: Right. So I spent a little time just now. I thought I made it fairly clear, right?

So what I don't do is, I don't do those regulatories. When I -- when

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you have a compound that's ready, we know all everything was great. We just need to make the pill and packaging.

We don't do that. We have no expertise. We don't -- I honestly have no interest in touching that in my personal career. But what everything else a drug development process requires, my lab does them all.

BY MR. SLATER:

Q. Do you know what an API is?

A. Yes.

Q. What is an API?

A. It's active pharmaceutical -- excuse me -- it's the ingredient. Sorry about that.

Q. In your career up to today --

A. Yeah.

Q. -- have you ever been involved in the development of the manufacturing process for an API that was actually sold?

A. Well, to answer your question like -- like yes or no question, right? So if this is like -- you ask me whether I have a drug on market. I thought I already told you. I hope

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I do. This moment I don't have any drug already be approved. We have multiple project on the way. I also have grant -- I'm not having yet. Hopefully, it will be founded. But have pending grant at FDA. They try -- I try to, you know, they are trying to fund me on something like you said to develop directly an API on the market, but not -- the grant is still pending. I cannot -- I hope I can get it.

Q. So up till today, you've never been involved in the development of an API that was actually sold on the market, correct?

A. No, it's not correct, right? So --

Q. So tell me -- then tell me --

MR. BERNARDO: Wait, wait.

BY MR. SLATER:

Q. -- which supply you have developed that's actually on the market?

MR. BERNARDO: Object to the form of the question, and he said that's not correct and clearly was --

MR. SLATER: Actually, you know what? I misstated my question actually, and I meant to ask about the

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manufacturing process.

BY MR. SLATER:

Q. Let me ask you this differently. So am I correct that up until today, you have not yet ever developed or been involved in the development of the manufacturing process for an API that was actually sold on the market? Have you ever done that up till today?

MR. BERNARDO: Object to the form of the question. Asked and answered.

BY MR. SLATER:

Q. It's a yes or no, sir.

MR. BERNARDO: Object to the form of the question.

THE WITNESS: You keep saying. You keep saying the question yes or noes. I also try to answer if it can be a yes or no, but it is not, right?

BY MR. SLATER:

Q. Have you --

A. I said --

Q. Have you --

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MR. BERNARDO: Object.

THE WITNESS: Yeah.

MR. BERNARDO: Let's stop interrupting the witness's question.

MR. SLATER: How about we suggest to our witness to answer the question directly? I think we both have objections here.

THE WITNESS: I -- I really trying, right? So I said if you ask me whether I have a drug on market after my name --

BY MR. SLATER:

Q. I'm not asking that.

A. I don't --

Q. Don't answer that, Doctor. I didn't ask you about your name or whether you own the drug. That's not the question I asked. So let's try to focus on the question now.

A. Yeah.

Q. Let's be precise.

A. Right.

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Q. Up until today, have you ever been involved in the development of the manufacturing process for any API that was actually sold on the market?

MR. BERNARDO: Object to the form of the question.

BY MR. SLATER:

Q. Yes or no. Have you done that or have you not done it?

A. Yeah. So I think I get the question. If you ask me whether any of the market drug at this moment was developed by me, the answer is, no, I haven't developed any drug that is sold on market at this moment. I hope my next drug will be sold on market next year or very soon. We are doing those, but I hope it's in the near future. If you say right now, Dr. Xue, if you have any drug already sold or you involve in any compound that is already be sold on market, it's not, but it doesn't mean I'm not doing those, right?

MR. BERNARDO: Adam, we've

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been going about an hour and 15. If this is a good breaking point?

MR. SLATER: I'm ready to keep going. So you guys like to do your hour break. You do whatever you want. If you want to stop the deposition and take a break, you have the right to do it. I don't need a break.

MR. BERNARDO: Dr. Xue, would you like a break?

THE WITNESS: Yes.

MR. BERNARDO: Okay. We'll take a break.

MR. SLATER: See you in 10 minutes.

THE VIDEOGRAPHER: Time right now is 11:17 a.m. We're off the record.

(Recess.)

THE VIDEOGRAPHER: Time right now is 11:29 a.m. We're back on the record.

BY MR. SLATER:

Q. Dr. Xue, do you utilize gas chromatography in your lab?

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A. In my lab, we don't use gas chromatography.

Q. Have you ever used gas chromatography for any of your work?

A. In graduate school, we used GC for some works when I was a graduate student. But, you know, in general speaking, because the nature of my research, we work on molecules that are not, like very small, like a solvent size.

So we do mass spec. We -- we do chromatography but usually liquid chromatography. They are same concept but different nature because the requirement of the size of the molecule.

Q. You utilize -- rephrase.

Do you use liquid chromatography in your -- in your work?

A. Yes.

Q. Do you use --

A. Instead of GC.

Q. Do you use liquid chromatography-mass spectrometry in your work?

A. I do use L -- we call it LC-MS -- liquid chromatography-MS in my work a lot.

Q. Do you operate the LC-MS machine or does someone else do that?

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A. I sometimes do that myself. Sometimes my student do them. Sometimes if it's high-end experiment, the collaborators in the mass spec center will do that themselves just to protect the improvement.

Q. Have you ever used any form of chromatography or mass spectrometry to try to identify a nitrosamine in a substance?

A. I never used -- you said chromatography -- either GC or LC to identify nitrosamine in my career.

Q. Have you ever used mass spectrometry to try to isolate or identify a nitrosamine?

A. I never in my career do that.

Q. Do you hold yourself out as an expert with regard to the formation and identification of nitrosamines?

A. You're asking I view myself as an expert for the formation and you said isolation as well for nitrosamine?

Q. Do you hold yourself out as an expert with regard to the identification and formation of nitrosamines?

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A. Thank you for repeating.

For nitrosamines specifically as a class of compound, I never did in my research. But in term of small molecule characterization and formation, we do that on daily basis. That's the nature the majority of our research do.

Q. When did you first learn of the NDMA and NDEA contamination of valsartan?

A. When I start to get involved in this case, I learned these two small molecules NDMA and NDEA contamination for valsartan API.

Q. According to the invoices that we were provided, your first meeting took place November 18, 2022 with Jessica and Allison.

Is that the first time you were contacted regarding this case?

A. I don't remember exactly the date I put. It's a while ago, but that was not the first time I was contacted.

Q. The date of the first meeting on your invoice is November 18, 2022.

When were you first contacted?

A. I believe it's probably three, maybe four days before that first meeting. I really

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honestly don't remember exact how many days.
Q. I don't know I need -- I don't need to know the exact date.
A. Okay. A few -- a few days before the meeting, Jessica Miller, Ms. Jessica Miller called me.
Q. So you first learned about the NDMA and NDEA contamination of valsartan in November 2022, correct?
A. Yes.
Q. In terms of the root cause for the formation of the NDMA -- you understand what root cause means?
A. If I understand correctly, root cause is like why. Is that the correct meaning of root cause?
Q. We can go with that for now.
A. Okay. Thank you.
Q. If we boil down the root cause to the very simple, the most -- the most fundamental reason why this, the NDMA formed in the zinc chloride process --
A. Your voice was chopped off because it was -- I think the Internet. Can you repeat

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what you just say?
Q. Sure.
Was the quenching of valsartan with sodium nitrite part of the root cause for the creation of the NDMA in the zinc chloride process?
A. I apologize, but just now your voice was still -- you freeze for like three seconds.
MR. SLATER: Am I freezing?
BY MR. SLATER:
Q. Might be on your end.
MR. BERNARDO: I think, Dr. Xue, it might be on your end because he was pretty clear on my end.
THE WITNESS: I heard you talk about sodium nitrate, but before that there were three second I didn't quite hear what you say.
BY MR. SLATER:
Q. Was the quenching with sodium nitrite as part of the zinc chloride process an important part of why the NDMA formed?
MR. BERNARDO: Object to the form of the question. Vague.
Go on.

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THE WITNESS: The quenching process of the -- you said the zinc chloride process, right?
BY MR. SLATER:
Q. Let me start over.
A. Okay.
Q. You know what? Actually, I'm not going to waste my time with this.
Let's now talk about a couple other things.
In your report, at one point you talk about reaction environments.
When you use the term a "reaction environment," would an example of a reaction environment be the zinc chloride process?
A. You want me to provide an example or you want --
Q. No. I just want to know if that's -- if my understanding is correct or not.
A. What was your understanding? So you --
Q. Is an example of a reaction environment the zinc chloride process?
A. A zinc chloride process is multiple

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step. It's -- I think we can call it four or five steps, right? Reaction in the environment is a specific set of conditions that's specific for the particular reaction.
It's -- it's -- I think for zinc chloride process, it's too big of a scope for environment because you want to -- you want to be more specific on what specific reaction you talk about.
Q. Would the tetrazole ring formation step of the zinc chloride process be an example of a reaction environment?
A. Yes, you can say that.
Q. Would the quenching step be a reaction environment?
A. Quenching step is also, yes. It's a -- we usually call it reaction conditions, but yeah. So environment is similar to conditions.
Q. One of the points that you make in your -- rephrase.
One of the subjects that you address in your report is the temperature at which the zinc chloride tetrazole ring formation step took place at.

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You discuss temperature in your report, right?
A. I did.
Q. And if I understand your opinion, it's your opinion that the temperature that the DMF was subjected to was too low for DMA to form.
Is that your opinion?
A. My opinion is ZHP at that moment, not now, but when they actually develop and use the zinc chloride process, they have no idea that DMF can actually decompose at the temperature that they run. I believe is 135 -- 335 degrees C.
Q. Are you aware that ZHP never even considered the question of whether or not the DMF could degrade during the process?
Are you aware they did not even consider the question or analyze it at all?
A. So you're asking --
MR. BERNARDO: Object to the question.
THE WITNESS: -- me to confirm that ZHP never aware that the decomposition of DMF could actually take place in their tetrazole reaction? Is

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that your question?
BY MR. SLATER:
Q. My question was different.
My question is: Are you aware that ZHP didn't even consider the question, didn't even think about the question of whether or not the DMF could degrade under the conditions of the zinc chloride process?
Are you aware they never even thought about that?
MR. BERNARDO: Object to the form of the question. Vague. Beyond the scope of his --
MR. SLATER: You're objecting? There's a stipulation that you entered into with me on this point.
MR. BERNARDO: Well, then, you don't need to ask this witness about it.
MR. SLATER: All right. Let's not go back and forth. You and I, we should not communicate during this deposition. It's not going well.
BY MR. SLATER:
Q. Doctor --

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MR. BERNARDO: Then you shouldn't engage me, Adam.
MR. SLATER: I'm not going to. That's the last time it will happen today.
MR. BERNARDO: Perfect.
BY MR. SLATER:
Q. Can you answer the question, Doctor?
A. I'm sorry. Can you repeat? I just got lost.
Q. Sure. Sure.
Are you aware that ZHP did not consider the question of whether or not DMF could degrade during the zinc chloride process to give off dimethylamine?
Are you aware they never even thought about the question of whether or not it could happen?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: Well, based on what I read, right, there's really not much available. They were not -- they didn't know and there's not actually

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reasonable to expect them to know.
BY MR. SLATER:
Q. Can you answer my question now?
A. So the question was, did I aware they didn't even consider, right?
I cannot speculate for other people whether they consider or not, but my research under my told me that, first of all, they didn't know. Second, they have not reasonably be expected to know this.
That's my -- I -- I cannot say -- I cannot speak for ZHP, right?
Q. Well, you're an expert in this case.
Do you understand that you're supposed to be objective?
MR. BERNARDO: Object to the form of the question. We're getting --
BY MR. SLATER:
Q. Let me ask the question differently because counsel didn't like my question.
Did you try to be objective in this case?
It's a simple yes or no. Did you try to be objective?

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A. Yes.
Q. So if you want to be an objective expert, you want to see, well, did ZHP do anything wrong?
That's one of the things you should have been thinking about to be an objective expert, right?
MR. BERNARDO: Object to the form of the question. Argumentative.
BY MR. SLATER:
Q. Correct?
A. I consider everything come to me to decide what I believe is correct or what I believe is wrong.
Q. Okay. In forming your opinions, you had to rely on the facts that were provided to you, right? You had to rely on the facts, correct?
A. For that I definitely agree, I rely on the fact. I rely on everything that actually provided I found around this topic.
Q. Okay. And in terms of the facts that you relied on, did you understand whether or not ZHP even considered the possibility that DMF

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could degrade potentially in the zinc chloride process? Did they even look at that question at all? Do you know? Yes or no.
A. Well, I -- I cannot say yes or no because how can I read other people's mind, right? I can only judge based on my understanding is they don't know, and they did not expected to know.
Q. Based on everything you read --
A. Right.
Q. -- what is your understanding about whether or not ZHP even thought about the question of whether or not the DMF could degrade during the zinc chloride process?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. What is your understanding of whether they even thought about the question at all?
A. My understanding or my feeling is they didn't.
Q. Your opinion is, if they thought about it, that you don't think they would have found out information that they later found out,

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right?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: I didn't quite understand your question.
BY MR. SLATER:
Q. Forget the question. We'll get -- we'll walk you through it with documents in front of your face. We'll do it that way when we get to that.
Okay. Are you an expert -- rephrase.
Do you believe that it's within your expertise to give an opinion as to whether or not ZHP should have thought about the question of whether or not the DMF could degrade during the zinc chloride process?
A. You're asking whether my opinion is ZHP should have thought of this degradation as a potential? You're asking that?
Q. You believe -- you believe that question, that you're an expert in answering that question?
A. I'm sorry. I don't think I clearly

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understand what you're asking because there's a couple of curves in the question itself.
Q. You're holding ourself out as an expert in organic chemistry in this case, right?
A. Yes.
Q. In terms of what the chemists at a drug manufacturing company called ZHP should have thought about in performing their risk assessment for the zinc chloride process, is that within your expertise what questions they should have thought about in developing the process?
A. Yes.
Q. Okay. In your opinion, should ZHP's -- rephrase.
In your opinion, should ZHP have at least thought about the question of whether or not DMF could introduce DMA into the zinc chloride process? Should they have considered the question?
A. I don't think there's available information for them during the time when this chemistry was developed to -- to trigger that thought. But, again, I cannot speak for them, but that's my understanding. So there's -- there's

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not enough to say that.
Q. Is one of your opinions -- well, rephrase.
Do you agree with me that the DMF was capable of degrading to form dimethylamine during the zinc chloride process? Yes or no.
A. You ask me now?
MR. BERNARDO: Wait, wait, wait.
BY MR. SLATER:
Q. I'm asking you now. As you sit here right now, is the answer yes or no?
MR. BERNARDO: Object to the form of the question. Vague.
Go on, Dr. Xue.
THE WITNESS: Right.
If you ask me now after I involve in this case and reading this reaction like hundred times over the last month. So now, yes, I know.
But we are not talk about the reaction happen right now, right? So I -- it's not also not talk. Maybe talk about ZHP when they try to develop this

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in 2013 or 2014, that's a totally different situation.
BY MR. SLATER:
Q. Did ZHP do any lab scale testing to replicate the temperatures the zinc chloride process would subject the DMF to in order to see whether or not DMA would form under those conditions?
I'm just asking if they did any tests of that question when they developed the zinc chloride process. Yes or no.
A. Well, again, there are things I read. If you want to discuss about a specific document, I prefer if you can put it up so we can discuss specifically.
But if you ask me off my head whether they did a lab scale testing of -- they did lab scale quality control when they actually do the risk assessment. When they try to make the switch from the -- the previous -- I think it's TEA process with quenching to the zinc chloride.
They did this assessment on the lab scale. I don't think they did this -- this -- this test about whether DMA is there. Because I

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already said, right? So they really have no reason to do so because they don't know. It could be a possible factor.
Q. Well, Dr. Xue.
A. Yes.
Q. You've been telling me what they could or could not have known. I haven't asked you that question.
I asked you if they did certain tests. So I would appreciate if you could limit your answers to the actual questions I ask instead of talking about things I'm not asking you about.
Can you do that for me, please?
MR. BERNARDO: And I would appreciate if your questions and your comments to the witness were not argumentative and if you would conduct yourself appropriately for an expert deposition.
BY MR. SLATER:
Q. Can we do that, Dr. Xue?
I would appreciate it if I ask a question about one thing if you don't talk about another thing. It would make the deposition go

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smoother, okay?
A. I'll try my best.
Q. Thank you.
Based on your review of the materials, you saw no evidence that ZHP actually did any tests, whether in the lab or at any other stage, where they ever actually tested to see if they subjected the DMF to the conditions it would be subjected to in the zinc chloride process whether or not it would degrade to give off dimethylamine.
No such test was performed to your knowledge, correct?
MR. BERNARDO: Object to the form of the question. Asked and answered.
Go ahead.
THE WITNESS: As I said, in test, they didn't test the formation of DMA during the process during the development. That's because at that time, they don't know that they need to test that.
BY MR. SLATER:

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Q. Why did you throw in the last part "that's because" when I didn't ask you about the reason? I just asked whether they did the test or not. So why did you throw in the other part?
A. I just want amore complete answer.
Q. But I didn't ask that question. So, I mean, the more complete answer could be everything you know. I just would appreciate if you would limit your answers to the question I ask.
MR. BERNARDO: Object.
THE WITNESS: I will keep that in mind. Thank you.
BY MR. SLATER:
Q. If I understand your opinion, it's that ZHP -- withdrawn.
In your opinion -- well, rephrase.
Is it your opinion that the only way that the dimethylamine was -- was introduced to the zinc chloride process was during the tetrazole step when the heating was to 135 plus or minus degrees Celsius? Is that when you believe the DMA was introduced to the process?
A. When I look at the process, right?

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So that's something the plaintiffs' expert point out. So I was just focused on that step and then look at this step.
Q. Is that your opinion?
MR. BERNARDO: He's finishing his answer, Adam, please.
THE WITNESS: I'm trying to finish. If you can let me. Thank you.
Right. So I -- I look at the -- the opinion from the -- the expert from the plaintiff side and that's what they were saying. So I tried to address that and I tried to.
Right now based on all the result already out there, yes. So I feel the degradation from DMF is likely the reason why.
Although I, as a scientist, before reading the study from FDA labs or ZHP or other companies, they have a conclusion. I won't just say for sure this will be the cause or that will be cause because I'm, you know, this must be -- there must be some scientific studies

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around this problem to be performed, and then that will give us a clear answer for this question.
BY MR. SLATER:
Q. Do you have an opinion, as you sit here right now, as to how the DMA was introduced to the zinc chloride process?
This is a yes-or-no question. I want to know if you have an opinion as to how it happened.
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. I just want to know if you have the opinion. I'm not even asking what the opinion is.
Yes or no. Do you have an opinion on that?
A. You ask me for opinion that DMA was formed during the zinc chloride --
Q. Not what I asked you, Doctor. You need to listen to my question, please.
Do you have an opinion as to how the DMA was introduced to the zinc chloride process? Yes or no.

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A. I do.
Q. In simple terms, what is your opinion as how the DMA was introduced to the zinc chloride process?
A. The DMA can actually form from different ways.
Q. I'm asking what your opinion is to a reasonable --
A. Right.
Q. -- degree of scientific certainty as to how it happened in the zinc chloride process.
If you have that opinion, tell me. If you don't know or you're not sure, you can say, "I don't know" or "I'm not sure."
A. Well, degradation of DMF is one of those, right? And there's other conditions involved in the tetrazole formation step. The zinc chloride. I don't know, right. So there might be. Also other factors.
As I said, that's my feeling. Because now we know DMA is in there and nobody does any project to figure out how, right? So my opinion is I said, yes, degradation from DMF is suspicious.

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Q. Is it your understanding that nobody has tried to figure out how the DMA got into the zinc chloride process?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: Are you asking me my understanding is nobody means?
BY MR. SLATER:
Q. Doctor, you just said to me nobody tried to figure it out. I'm literally repeating your answer to you.
A. No. At this -- well, I haven't seen any result from any publication or announcement saying what is the exact reason that dimethylamine was formed. I haven't seen that.
Q. Okay.
A. If you have a document, I'd like to see that document.
Q. Well, what I'm trying to figure out is what you know to form -- to support the opinions you've given in this case. My goal right now is not to educate you and get new opinions.
So I'm trying to figure out what you know now. Okay?

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A. What I know now is -- is -- is during the zinc chloride process, somehow during that zinc -- during that tetrazole formation step, there are dimethylamine formed. I don't know exactly because, again, I'm a scientist. Until I see a definite experimental evidence, I cannot see anything. I suspect that's the degradation of DMF maybe with some sort of assistance from other reagent used in combination. I don't know, but that's my -- my feeling at this moment.
Q. So you agree with me that DMF was capable of degrading at the temperatures it was exposed to during the zinc chloride process and forming dimethylamine, correct?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. You agree with that as you sit here right now, correct?
MR. BERNARDO: Object.
THE WITNESS: I don't agree. I think I made it clear.
This is one of the possibilities. It's a chance, I suspect.

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I use the word "suspect" that can be actually happen.
I also said that the other conditions involving the reaction can actually contribute, which nobody did research yet. Until we have some sort of publication on this case, I don't think I can agree with anybody's speculation.
BY MR. SLATER:
Q. So I'm going to come back to the question I asked you a few minutes ago because you're telling me there's possibilities, but you're not sure which one happened.
What I need to know is: Do you hold an opinion now to a reasonable degree of scientific certainty where you can say more likely than not the DMA was introduced to the zinc chloride process through this means?
Do you have an opinion as to that?
Not it could be a bunch of things, but do you have an opinion as to what it was that actually caused the DMA to be introduced to the zinc chloride process? Yes or no.
A. I don't have a specific reason to

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say exactly this must be the road that DMA has been formed during this step. I don't have that. Because how can I have something which no research has been done on this?
Q. All right. Let's go back to the deviation investigation report that we marked earlier.
What did we mark it as?
A. Which? Can you remind me the number again?
Q. Yeah, I can. It's Exhibit --
MR. BERNARDO: 5?
MR. SLATER: It's Exhibit 5. Exactly.
MR. BERNARDO: Wow.
BY MR. SLATER:
Q. And let's go to --
A. So can you remind me the number of the file? Number?
MR. BERNARDO: It's Exhibit 5, Dr. Xue.
THE WITNESS: Yeah, Exhibit file number 3.
MR. BERNARDO: Oh, I don't.

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THE WITNESS: On my list.
Can somebody?
BY MR. SLATER:
Q. Let's go in that document to page 170.
MR. BERNARDO: Adam, one second. He's asking -- I'm trying to look where -- he's trying to pull it up where --
THE WITNESS: 5 exhibit? Which one?
BY MR. SLATER:
Q. Exhibit 5, the deviation investigation report.
A. Number 5?
Okay. I'm on that report. Thank you.
Q. Let's go to page 9 of 236 within that report.
A. To you said page 9 of 236?
Q. Yeah. You see at the top right there? You see -- see on the screen, Doctor? Look on the screen.
A. Oh.

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Q. You see page 9?
A. Okay. Thank you for highlighting me that. Let me --
Q. You can also look at it on your screen. You can do whatever you want.
A. Okay.
Q. Do you see the page I'm asking you about, page 9 of 236?
A. I am.
Q. And you can see that on page 9 of 236, ZHP conducted lab scale trials.
You see that in the middle of the page? It says:
"For further confirmation, the following lab scale trials were designed and performed to verify the concluded formation mechanism of NDMA."
Do you see that?
A. I see that section and the Table 3-1.
Q. And it says:
"The amount of NDMA formed by quenching under different temperatures is shown in the table below."

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Do you see that?
A. I see that table, the conditions.
Q. And you see that they subjected the DMF plus zinc chloride to react at 135 degrees Celsius for 20 hours, and they talk about what they did and eventually added the sodium nitrite later.
Do you see that?
A. Yes.
Q. And you see the NDMA in parts per million that was produced by these various experiments?
A. There's a column called "NDMA (ppm)," right. That's the column you talk about, right?
Q. Right.
A. Okay.
Q. Right. Have you ever seen this page before right now?
A. Yeah, I don't remember exactly whether I see this page, but, yeah, I do read this document before.
Q. I didn't see anything in your report where you talked about the fact that ZHP actually

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performed lab scale trials where they proved that under the conditions of the zinc chloride process, NDMA would form from the DMF and the sodium nitrite.
Do you see that?
Let me withdraw it and ask it again.
I don't see any discussion in your report about the lab scale trials that were performed by ZHP to prove that the NDMA could form under the conditions of the zinc chloride process.
You don't talk about that in your report, right?
MR. BERNARDO: Object to the form of the question. Assumes facts.
THE WITNESS: I didn't talk about that in my report because I thought that's -- that's the best of fact, right?
So we already by the year of 2018 knew that these impurity can actually form as a side product in the reaction that they try to do for the tetrazole formation. I think that's the fact, right?
So I didn't know that I have

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to repeat what the fact is. And these experiment was this period is to try to figure out, as you highlight here, at different conditions how much of NDMA can form.

I think that that's kind of a backward looking back from 2018. Say, oh, now we know under the condition that I perform the tetrazole formation reaction, there is. That's a conclusion already draw, and then they look back to try to change the condition to figure out which parameter maybe play a bigger role.

And it looks like to me all the six entries they actually did, they all form some, to some extent, in ppm value percentage some -- some DMAs.

So I don't see why there's any conflict here. So I -- I don't see why I should actually include this citing this table because that's already be the fact that by the time when they actually look back.

BY MR. SLATER:

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Q. My question is very simple.

Nowhere in your report do you talk about the fact that ZHP did lab scale testing to prove that the DMF could degrade, form DMA, and then the sodium nitrite could combine with that to create NDMA.

You don't discuss the fact that they did those tests in your report, correct?

I'm not asking why you didn't do it. I just want to confirm you didn't do it, right?

MR. BERNARDO: Objection.

THE WITNESS: Well, I do --

MR. BERNARDO: Wait, wait, wait, Dr. Xue.

Object to the form of the question. Argumentative.

Go ahead, Dr. Xue.

BY MR. SLATER:

Q. I just want to know. Did I miss it? Is it in your report or not? Just please. It's a yes-or-no question.

A. You missed because it's a time matter, right? It just like you run reaction, you have to know the parameter. Here we discuss the

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topic, we have to know what we talk about, right?

So this is in 2018 when the whole thing showed up. Everybody understand, including myself now, right? So this reaction could actually lead to this impurity. Nobody want that. ZHP didn't want it. Nobody want that, but it happen.

Now, when we look back to figure, oh, what is the cause? Why this actually happen? They did this whole bunch of analysis.

Actually, in my lab, we do this as well, right? So we cannot design a project that goes just like you design. Unfortunately, science is not like that, right?

So happens a lot of time, if not all the project, that at the end or on the way you will find out the reaction didn't go like you will happen, right? So you isolate and characterize and find, okay, there is impurity, unfortunately, formed. It's not something designed. It cost me time and money, but we need to look back to see how, what is the reason cause this.

So to do that, the general exercise what I do, a lot of my colleagues, everybody in my

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lab they also do is just to -- to see, okay, then let's see what is a possible reason to cause this. I believe this is what they did, right?

So, you know, I really don't see why I should actually include this piece in there. So what I want to prove? I don't see a point that can actually bring to me, right?

We are not talk about, right, if you tell me, okay, this is a table that ZHP or anybody at ZHP they actually did in 20 -- in 2007 or 2010 even, right? So they know this already. That's totally a different story, right? But we not talk about that every.

I hope I address your question.

Q. Okay. Simple yes-or-no question.

Did you talk about ZHP's testing as shown on page 9 of this deviation investigation report in your report? Yes or no.

I just want to know if you talked about it or not.

MR. BERNARDO: Dr. Xue, please listen to Mr. Slater's question, right?

THE WITNESS: I didn't talk about this experiment specifically in my

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report.
BY MR. SLATER:
Q. In fact, you didn't talk about any experiments performed by ZHP in your report, correct?
A. So if I understand your question, you are asking do I mention any experiments ZHP performed in my report? That was your question, right?
Q. Right. Yes-or-no question.
A. I mentioned everything. If you read my report you said, right? I mention every single, all four of their processes. Every step I actually have joined all those reaction in my report. I mention every reaction they perform, how they do it, and what the conditions are. When they actually make any change, what kind of parameter they actually change they follow. They perform all these testings. I mention that.
If you ask me whether these six reaction you show in this table right now? I didn't mention that. As I explain to you just now, I don't see why I should mention that in my report.

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Q. So if I understand your opinion, ZHP proved after the fact that the DMF could degrade to give off dimethylamine, but there's no way that they would have known that before they developed the process or while they used the process. So they were never on notice that DMA might be introduced to the zinc chloride process; is that correct?
MR. BERNARDO: Object to the form of the question and the characterization of his testimony.
BY MR. SLATER:
Q. Is that your opinion?
MR. BERNARDO: Go ahead.
THE WITNESS: So I'm here trying to address the -- the expert from the plaintiff side, right?
So my opinion, I think, is very clear I mention about these. They have no -- they don't know and they have not reasonably be able to expect to know these are actually can trigger the issue.
BY MR. SLATER:
Q. Did ZHP consider the fact -- well,

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let me ask you this.
Did you consider -- I don't want to do it that way, actually.
Did ZHP take into consideration whether or not DMA, which is dimethylamine, could be an impurity of commercially purchased DMF such that they could introduce DMA into the zinc chloride process as an impurity when they put the DMF into the process? Did they consider that possibility?
MR. BERNARDO: Object to the form of the question. Compound.
Go ahead.
THE WITNESS: So now we are changing to from formation from a degradation to -- to you imply there's a contamination already before they actually perform the reaction in common with the DMF? That what -- that's what you refer to?
BY MR. SLATER:
Q. Did ZHP consider that possibility, to your knowledge?
A. To my knowledge, I don't think they

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did.
Q. That's all I asked.
A. Thank you. I got one.
Q. In forming your opinions, did you consider the possibility that DMA could have been introduced to the zinc chloride process as an impurity of the DMF?
A. You're asking me when I formed my opinion whether I considered contamination of DMF by DMA? You ask me about that? I just want to confirm that's what the question you're asking.
Q. Yes. When you formed your opinion, did you consider the possibility that DMA could be an impurity of commercially purchased DMF and be introduced to the zinc chloride process as an impurity of the DMF?
A. Right.
Q. Did you consider that possibility?
A. Right. So when I --
Q. It's a yes-or-no question. I just want to know if you considered that possibility or not. Yes or no.
MR. BERNARDO: Objection.
THE WITNESS: When I formed

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my opinion, I mostly address what the -- the expert from the plaintiff side, right? So I don't recall they actually raise this in their report. That's the reason why when I formed my opinion, I didn't really trying to include this section or this study, this discussion in my report.

I think so far the only -- because there's so many documents, right? But the only document that I can -- I can recall that -- that sort of addressed this was, I think during the root cause study, ZHP did some sort of analysis of the DMF solvent they use in their processes.

They found the, you know -- I'm not regulatory science, right, scientist, but I know they found the -- the grade of the DMF they used was -- was good. So they didn't actually find high ppm. I believe both DMA and DEA was -- was way below the bar. I don't remember -- recall the specific numbers.

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So that's the only reason. That's the only avenues, and then I don't think any of -- I might be wrong, but I don't think I read any of the -- the report from the plaintiff side mention those. So I didn't just -- just went on to address that directly.

So I disagree that they didn't do any study or they don't know.

BY MR. SLATER:

Q. Did ZHP know that the DMF it was purchasing could have DMA as an impurity and that it could be introduced into the zinc chloride process as an impurity of the DMF?

Did ZHP know that when they --

A. Well, as I said --

Q. -- developed and used that process? Yes or no.

I just want to know. What do you know about that? Yes or no. Did they know?

MR. BERNARDO: Object to the form of the question. Foundation.

Go ahead.

THE WITNESS: Well, I don't

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know because I can -- I cannot have know -- any reason to know whether ZHP know by then.

BY MR. SLATER:

Q. You don't know. That's fine. It's okay. Based on everything you read, you don't know. That's your answer. It's fine.

A. Yeah, I hope I can offer something. That's why.

MR. SLATER: Let's -- let's put this aside for a second and put up as exhibit -- what are we up to 6 or 7?

All right. Let's put up as Exhibit 6 the World Health Organization publication from 2001 titled "N,N-Dimethylformamide."

THE WITNESS: Are you putting it up?

(Document marked for identification as Xue Exhibit 7.)

BY MR. SLATER:

Q. We're putting it into the thing so you can download it. We're going to put it on the screen. I'm going to show you one page.

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So, first of all, are you familiar with this document? Have you seen this?

A. I think I saw this before.

Q. Okay. This would be scientifically knowable to somebody who was developing the zinc chloride process at ZHP, right?

MR. BERNARDO: Object to the form of the question.

BY MR. SLATER:

Q. This document would be available to somebody who's a chemist at ZHP, right?

A. Well, as you just described, the document is available. I don't know whether ZHP has read that or not. I cannot speak for other people. I read this before. It is available as you described.

Q. Let's go to page 5.

A. Okay. 5 of the document, right?

Q. Yep. It's right there on the screen. Paragraph 2. Or not. Rephrase.

Looking at page 5 of this publication, Section 2 titled "Identity and Physical/Chemical Properties" in the bottom, right.

Do you see that?
It's on the screen, Doctor. It's right in front of you on the screen.
Do you see it?
A. Yeah. Yeah. Yeah. I mean, I'm sorry. I was looking at my -- my own trying to.
Yeah, go ahead.
Q. And there's a paragraph that talks about N,N-Dimethylformamide.
Do you see that first paragraph?
A. The second last paragraph from the -- on the right column, right?
Q. Correct.
A. Okay. I saw that.
Q. The last sentence of that paragraph says:
"DMF sold commercially contains trace amounts of methanol, water, formic acid, and dimethylamine." And there's a citation to 1994.
Do you see what I just read?
A. I saw what you just read.
Q. Before I just showed you that, were you aware that DMF sold commercially contains trace amounts of methanol, water, formic acid, and



dimethylamine? Did you know that before right now?
A. Are you -- if you ask me specifically of these four substance -- methanol, water, formic acid, and dimethylamine -- do I know whether these are the four contamination that can possibly contains in the -- in the DMF sold commercially, I probably don't know the four off my head. But as a --
Q. Did you know -- go ahead.
A. Sorry. Can I -- can I go ahead? Yeah.
But as an organic chemist, right, we buy solvents like DMF or other solvent all the time, right? So they always have a certificate come along with it. So that's where we actually go for it.
We -- we usually, like my lab, if we want a 99.9 percent, so we actually trust what the vendor told us and we read the -- we call it a Safety Data Sheet to actually learn this information.
But if you ask me whether I know this particular sentence or these four specific



small molecules can actually present in DMF, I don't know.
Q. Okay. In forming your opinions in this case --
A. Right.
Q. -- did you consider the fact that DMF sold commercially contains trace amounts of dimethylamine such that DMA -- well, let me stop there. Let me ask it again.
When you formed your opinion in this case, did you take into account the fact that DMF sold commercially contains trace amounts of dimethylamine?
MR. BERNARDO: Object to the form of the question. Compound. Asked and answered.
Go ahead, Dr. Xue.
BY MR. SLATER:
Q. Just want to know if you considered that when you formed your opinions in this case.
A. Well, when we buy or when we use any chemical in practice as a chemist, right? So you always rely on the -- on the certificate you got from the vendor, right?



So this sentence by reading says "sold commercially contains trace amount" these. First of all, trace amount is a very vague. Like 1 ppm or .001 ppm of each, that should be listed specifically for each one of the chemicals that you order.
So this is just, I think, is a summary from the WHO. That really does not tell you a specific product for me. Because if I'm doing my research running my reaction, if I want to buy something that I care, I have to go specifically to that website and downloading the corresponding data sheet or called Safety Data Sheet to -- to read what exactly in there.
So I don't take for granted that this is the four compound that must be contained in my DMF and, again, trace is a very vague number they will not use.
Q. Doctor.
A. Yes.
Q. When you formed your opinion, did you take into account the possibility that the DMA was introduced into the zinc chloride process as an impurity or contaminant of the commercially

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purchased DMF that was used? Yes or no.
A. I didn't because ZHP showed during their study their DMF doesn't contain dimethylamine.
Q. Okay. Now, next question.
You said that you worked --
A. But can I -- can I -- can I say something, too?
Q. I asked you -- see, here's the problem, Doctor. I asked a simple question. You answered it. I don't know why you want to talk about something else.
I didn't ask why. I'm not asking for an explanation. I'm never going to finish this deposition if you give me long stories about things I'm not asking about.
A. I did not. I just want to point out one thing. While you're on this document, I was on the second screen I saw something. Can I raise that?
Q. No. I'm not asking about something on the second screen. I asked you a simple question that's not even about this document at this point.

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A. But you don't allow me to -- to raise that point? That's what you're saying?
Q. I want an answer to my question, and you answered. You're not answering my question. My question -- let's take this down off the screen because I'm not even asking about this document.
When you formed your opinions, did you take into account the possibility that the DMA was introduced to the zinc chloride process as a preexisting impurity or contaminant of the commercially purchased DMF that was used?
You already said you did not take that into account, correct?
A. I didn't. I said -- what I said --
Q. That's all I asked. I just wanted to know if you took it --
A. Can I explain?
Q. -- into account, and you said no.
A. Can I explain?
Q. I understand why, but I don't -- I don't need an explanation. I'm going to go on to the next question now.
A. No, that was not my -- my statement. That's not my testimony.

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I didn't consider, one, because ZHP did the root cause study to show that their DMF didn't contain, and they have a specific number listed. They are not -- they are below 10 ppm, but they didn't do any.
And plus, as I already mentioned, the expert from the plaintiff side during their -- during their -- in their opinions or in their writing the report, they didn't address this. So that's why I didn't put it in there. That's the only evidence I saw. So I didn't -- I didn't address that in my report.
But you want me to -- to agree with you that, you know, I didn't consider this. I want to let you know the truth. That's what I -- I actually put down.
And just now before I can finish, you take down that PowerPoint or not -- that document. I think it's not quite fair because I really just now see something.
I mean, it's actually the page right next to that page that says actually the temperatures in excess of 350 degrees C are required for DMF to decompose into carbon monoxide

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and dimethylamine. That's also on the same exact document that you just showed me. I think I have the right to point it out.
So if we all agree, WHO is -- is out there and it's up there. Everybody should actually respect the WHO. So I think we need also think about WHO in their same document. If you put it up again on that -- on that file you just -- you just take down quickly.
On page 6 of that document on the -- on the left column on the top paragraph it says what I just read. "Temperatures in excess of 350 degrees C." That's way, way above the condition that ZHP been using to perform their tetrazole formation reaction actually are required for DMF to decompose.
So I want to -- I want to read that to you so you have a record. So that's something I want to point out.
Q. You said something earlier.
You said that you, as a -- as a chemist -- organic chemist, when you purchase substances, you look at the Material Safety Data Sheet.

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Remember you said that?
A. I usually do.
Q. Are you familiar what a Certificate of Analysis is?
A. I don't know off my head what Certificate of Analysis mean.
Q. One of the things you said is, as an organic chemist, you should always rely on the certificate from the vendor as to what is in the substance you purchased, right?
A. We -- we -- if we need information from there, like if I want to figure out the decomposition of DMF if I buy it, I will just go there to look. That's my -- that's my side. I usually do. I'm not saying everybody else should do the same. That's my practice. I teach my student the same way.
Q. You would expect that the chemists at ZHP looked at the Certificate of Analysis to know the composition of the DMF they were purchasing to put into the zinc chloride process, right?
A. Well, I cannot speculate for any other people than myself. I told you I do that.

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Q. You have no opinion on that?
A. Well, my opinion is I do that and my student in my lab, they all do that because I advise them to do so. I -- I cannot force other people to do the same way as I do.
Q. Do you have an opinion as to whether the chemists at ZHP should have looked at the Certificate of Analysis for the DMF that they purchased for use in the zinc chloride process?
I just want to know if you have an opinion on that or not. If you, you do. If you don't, you can say, "I don't have an opinion."
A. I don't know what other people do.
Q. Have you seen any Certificates of Analysis or Material Safety Data Sheets regarding the DMF or any of the other substances that were used in the zinc chloride process or the TEA with sodium nitrite quenching process?
A. You ask me if I went in to look at the data sheet?
Q. I'm asking if that was provided to you, if it's one of the materials you reviewed in forming your opinions in this case.
A. Well, I --

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Q. Yes or no. Did you or not?
A. This is not a yes-or-no question. Can you let me finish?
I told you early on, right, I was provided a lot of document. I also did my own research. So to go out to look for the data sheet was my own practice. Nobody provide this to me, and this is my routine exercise from -- for anything that I do.
Q. Right.
Did you do that here?
A. I'm sorry. For which one?
Q. Did you -- did you do any research to see what the Certificate of Analysis or the Material Safety Data Sheet or any information from the manufacturers of the DMF might have said about the contents of the DMF that was purchased by ZHP?
Did you do any research on that? Yes or no.
A. I did research myself to see what's available for DMF from the site that I purchase DMF. I don't know. I have no reason to know what ZHP has been purchased from. So I --
Q. Is that -- is that in your reliance

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list? Did you list that you did that research and what you found when you looked at your supplier's website on DMF?
MR. BERNARDO: Object to the form of the question. Vague.
BY MR. SLATER:
Q. I just want to know.
Did you disclose it in your report or on your reliance list? Yes or no.
MR. BERNARDO: Object to the --
THE WITNESS: My reliance list has so many things. I disclose everything that is provide to me from the counsel. I disclose everything that I use to form my opinion.
BY MR. SLATER:
Q. Did you disclose everything you found --
A. If you push me to the corner --
Q. -- in your report?
A. Well, if you push me to the corner like this to say what I disclose exactly let me memorize at this moment everything, I don't think

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is fair.
Q. Doctor, I didn't ask you to disclose everything to me right now.
I'm asking you. You just told me you did research on the website of your DMF supplier for your lab.
A. Right.
Q. Did you do that in connection with this case?
A. I did search DMF.
Q. What did you find?
A. I'm sorry?
Q. What did you find?
A. I find a documentation that is called a Safety Data Sheet for my DMF search. I see the parameters that in there. I didn't look at every detail, but I did find in there they also mention the degradation temperature is 350 degrees C.
Q. Did they talk about in that document the potential for impurities including dimethylamine?
A. I don't remember those.
Q. You don't remember.

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Did you look at the Certificate of Analysis for the contents of the DMF, which is something that would be different from the Material Safety Data Sheet? Did you look for that document?
A. Honestly, I don't even know what the document is. If you have example, if you put it up, I will probably be --
Q. No.
A. -- report that.
Q. Okay. Where -- so you did research. You looked at a website, and I just want to know.
Where is that listed in your report or on your list of materials reviewed? Is that listed anywhere?
The DMF supplier's website. I just want to know. Is it listed in your report or your reliance list?
A. Well, I --
Q. It's a yes-or-no question.
A. I don't know at this moment. I say I never hide anything. If I consider everything, I put in the report or put in the list of consideration. I...

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Q. Okay.
A. I may use some as my citations, may use others as citations. For that I choose, but I didn't hide anything.
Q. Well, I didn't ask if you hid anything. I just asked if you mentioned it or listed it anywhere in your report.
A. Well, as I mentioned to you then, I really off my head I don't recall all these details. I hope you don't push me to do that.
Q. Let's look at -- let's go back to the deviation investigation report.
A. Can you remind me the number again?
Q. It's Exhibit 5, sir.
A. Thank you so much.
Q. Go to page 157 of 236.
Looking at the bottom half of the page.
A. Sorry. I'm -- I'm moving slower than you.
Q. It's right on the screen. I mean, you can see it. It's right on the screen.
A. I understand it's on the screen. I'm sorry. I also want to see that report, the

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document on my own so I know what I'm reading. I don't want to make any mistake.
Q. Scroll down a tiny bit just so we can see the middle of the page also. No, the other way.
A. Are you talking about page 153?
Q. 157.
A. Oh, 7.
Okay. 57 -- 157 of 236.
Q. All right. So looking right at the middle of the page, it talks about "Discussion on Suppliers of DMF" and there's "Supplier Information."
Do you see that?
A. I can read there's supplier information there.
Q. And the paragraph says:
"Huahai has written procedure 'API Supplier Procedure of Raw Materials SMP-018.08' to regulate the selection, examination, assessment, evaluation and audit of suppliers. There had been five suppliers of DMF (correspond to two manufacturers) in Huahai since 2010. All of them meet the requirements of the procedure by

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reviewing supplier information. The details are in Table 4-32 as follows."

Do you see what I just read?

A. Yes, I did see the section that you read.

Q. And if you look at the table below, it lists the suppliers and the manufacturers of the DMF.

Do you see that?

A. I see there's a Table 3 columns, right? They talk about the suppliers, manufacturer, and the approval dates. Yes.

Q. Okay. And you see one of the companies is Shandong Hualu Hengsheng Chemicals Company, Limited? Do you see that's one of the manufacturers of the DMF that was used by ZHP?

A. I --

Q. In the Manufacturer column, if you read the manufacturers' names, there's two manufacturers. One of them is Shandong Hualu Hengsheng Chemicals.

Do you see them?

A. You talk about the last one in the column. Is that the --

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Q. It's the column that -- there's a column that says "Manufacturer."

Do you see the column?

A. Right. I see within the column you talk about the last row.

Q. Yes.

A. Okay. Yeah.

Q. If you go to the next page, you'll see they're also listed there, too, okay? But that's Shandong. I'm going to call them Shandong.

Okay?

A. So I --

Q. Doctor, I don't know what we're doing. Let me -- let me do this.

Do you see one of the manufacturers is Shandong Hualu --

A. Yes.

Q. -- Hengsheng Chemicals?

A. I do. You also talk about next page, right?

Q. Forget that. Forget it. I'm asking you to read that.

A. Okay. Yeah.

Q. You see Shandong is one of the

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manufacturers?

A. Based on reading, that is. Yes.

MR. SLATER: Okay. Let's put up the Shandong document now.

I would -- I would like to -- well, do you have it all as one document?

Make it into one document and let's put it up. Put up whatever you have. I just want to move through this.

I'd rather have done it as one, but we'll do it all. I just want to move through this.

BY MR. SLATER:

Q. What we did, Doctor, is we went on the Internet and we got the Certificate of Analysis for Shandong's DMF.

And I'm just going to walk you through what we did.

This is the website we went to. Okay? This is Shandong's website.

A. I'm sorry. Are you talking about the PDF you're showing me now?

Q. Yeah, this is Exhibit what?

A. It's written in Japanese and

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English?

Q. What I'm showing you is a website -- hold on.

All right, Doctor, we're going to cut to the chase here. We're going to put up on the screen. What exhibit number are we up to?

A. Number --

Q. I'm not asking you, Doctor. Sorry.

A. Sorry.

MR. SLATER: What exhibit is this?

Okay. This is Exhibit 7.

(Document marked for identification as Xue Exhibit 7.)

MR. SLATER: Two pages?

BY MR. SLATER:

Q. Doctor, on the screen is Exhibit 7. It's a Certificate of Analysis that we obtained for Shandong's DMF.

Do you see that on the screen?

MR. BERNARDO: I'm just going to reserve my objection to this. I don't have a copy of it to look at yet, but just reserve. Go on.

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BY MR. SLATER:
Q. Okay.
A. Well, I can -- I can see the document. This, again, is also new to me. I haven't seen this document before.
Q. Do you see that it has a list -- a list of specifications and results and shows that there's dimethylamine at 1 part per million in the DMF from Shandong?
MR. BERNARDO: I object to the form of the question.
And, Adam, can you just display so we all know what the date of this document is at least? I don't have a copy of it.
MR. SLATER: I don't know the date of the document. I don't know what that is.
MR. BERNARDO: You're asking the witness a question.
MR. SLATER: Hey, I don't need to be laughed. Okay? So you want to do that, do that with somebody else.
MR. BERNARDO: Okay. Adam,

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there's not an iota of laughter in what I said and you know that, and let's just -- come on, Adam.
MR. SLATER: I'm watching your face. I want to continue the deposition. You guys --
MR. BERNARDO: I do, too, but don't comment and claim I'm laughing when I'm not.
MR. SLATER: Hey, you're the one who asked my expert if he's seen the Certificates of Analysis for the DMF that to our knowledge was never produced by your client. Okay?
MR. BERNARDO: Let's move on.
MR. SLATER: Unless you want to make a representation that -- hey, do you want to tell us right now whether the Certificate of Analysis for the DMF were actually produced? Because our understanding is they weren't and we're not sure why.
MR. BERNARDO: Okay. Let's move on and ask the witness.

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MR. SLATER: So the answer is you don't want to answer whether you actually produced them. So nobody else --
MR. BERNARDO: So the answer is that I'm not being deposed here, Adam. I'm simply asking for the date of the document that we're all looking at on the screen so I understand what we're looking at.
BY MR. SLATER:
Q. I'm showing you a Certificate of Analysis from Shandong Hualu-Hengsheng Chemical Co. for dimethylformamide shows that it has dimethylamine --
MR. BERNARDO: Objection.
BY MR. SLATER:
Q. -- consistent with that publication we showed you before saying that dimethylamine is an impurity of DMF.
Do you see that on the screen?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: I'm sorry.

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The -- the -- on my screen says "Internet unstable." I really didn't. I only hear you said "DMF" at the end. I didn't hear the question at all. Can you please repeat your question?
BY MR. SLATER:
Q. Do you see on the Certificate of Analysis it shows that the DMF contains dimethylamine?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: On the table that you show me on this document, which I've never seen before, there is entry a couple dimethylamine ppm.
BY MR. SLATER:
Q. Do you agree with me that the chemists at ZHP should have been aware that DMA can be an impurity or a contaminant of the DMF that they were using? Should have been aware of that possibility? Should they have thought about that?
MR. BERNARDO: Object to the form of the question. Vague. Assumes

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facts not in evidence.
BY MR. SLATER:
Q. Or do you have no opinion on that question?
A. Well, first of all, this document, when did you get this document?
Q. Doctor, I just asked you a question not about this document.
A. Because this document is not very clear to me. So what --
Q. Doctor, I didn't ask you about the document. So I'm not really sure why you're talking about it.
Take it down.
A. No. What date that you download this document. Is the document from --
Q. The document was downloaded in the last few days.
A. Okay. So -- so that means this is the --
Q. You want to answer me? I don't know why you're talking to me about this because that's not what I asked you. I asked you a very direct question.

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A. I want -- I want to answer your question so that's why.
Q. Okay. So let me ask it and you'll answer it. Okay?
A. Okay.
Q. Should the chemists at ZHP have considered the possibility that the DMF they were using in the zinc chloride process contained DMA? Yes or no.
MR. BERNARDO: Object to the form of the question. Vague. Asked and answered.
Go ahead.
BY MR. SLATER:
Q. Or you don't have an opinion.
A. Well, as I just mentioned, right? So this, I need to know if you show a document. You said a few -- a few days ago this document is download from this website.
I need to know whether this document is all the same document is also available when they actually purchased. You show me two documents, right? I just want trying to be scientific here.

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Q. You're not being scientific. You're being evasive.
A. Well --
MR. BERNARDO: Object to the form of the question. Let's stop with the characterizations here and arguments.
MR. SLATER: I asked a very simple question.
THE WITNESS: Can you let me finish?
MR. SLATER: Maybe you can ask your witness to answer the question I asked.
THE WITNESS: Can you please let me finish?
MR. SLATER: It has nothing to do with the document.
MR. BERNARDO: Let's -- let's -- let's stop talking over each other. This is becoming harassing and I'm, like, let's just take a break and cool down because this is --
MR. SLATER: No, we're not taking a break right now. I'm getting --

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I have a pending question. I want it answered.
MR. BERNARDO: Answer the question and then we're going to take a break.
BY MR. SLATER:
Q. It's a very simple question, Doctor.
A. Can I speak now?
Q. No, you can't because I'm asking the question again.
A. Right. So --
Q. Can you answer it with a yes-or-no answer?
A. I need to first understand the document and then I will answer the question.
MR. BERNARDO: Dr. Xue, let -- let -- let Mr. Slater ask his question. Forget about the document. Okay?
BY MR. SLATER:
Q. Should the chemists at ZHP have considered the possibility that the DMF that they were using in the zinc chloride process could contain DMA as an impurity or contaminant of the DMF? Yes or no, or you have no opinion.

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A. My opinion is they could, but as I said -- can I -- can I speak now?
Q. I don't know what that means "they could."
Is the answer, yes, they should have considered it, no, they shouldn't have, or you have no opinion?
A. They should, but I --
Q. You answered.
A. Now, can I speak for myself?
Q. I'd rather -- look, I can't stop you from talking, but you've answered my question.
A. No.
Q. No. You told me your opinion.
A. You said the scope because every of my opinion has a scope, right?
So you showed me one document first. On the document there shows this -- this company was a supplier for ZHP back to the year 2011 June, right?
And then you showed me a second document where you told me you guys download a few days ago that shows what the -- the analysis or the data of the product of a few days ago, right?

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So now you want -- you want to ask me question about whether these two document can talk to each other. I can't because I have to understand and learn what is the specific situation you described to me. Okay?
So, again, the company is supply -- one of the suppliers back to 2011, and now you show me something that is they have a data sheet right now have this. I have no reason to speculate, but I don't know what their data sheet will be like at the year that you talk about they -- they serve as a supplier for -- for ZHP.
So I, as the scientist, I have to be very clear about what I'm -- what I'm talking about. You talk about one thing over 10 years ago. Now you talk about this new discovery three days ago and you say -- you try to say this is the same thing.
I can't really comment on that. That's why I was pausing. I need to actually really understand the situation that you describe. If you show me a document back to then or I don't even know whether this company would still be the best -- the supplier or they -- they actually have

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the -- the same DMF actually have same kind of quality data sheet.
Q. If the chemists at ZHP knew that DMA could be introduced to the zinc chloride process as an impurity of the DMF, they needed to take that into account when they did a risk assessment for the process, correct?
MR. BERNARDO: Object to the form of the question. Calls for speculation.
BY MR. SLATER:
Q. Do you have an opinion, yes or no, or you don't have an opinion?
A. So fact they don't know, right? I don't see any direct evidence to show that back then at the year 2011 they know. Because what you just show me is a website you show me three days ago, right? I don't know how many versions of the website has been evolved over the past decades. I really don't know. I cannot comment.
And as I said multiple times earlier on, too, I'm here as an expert in organic chemistry trying to address what the expert from the plaintiff side actually raised as their

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comments, right?
So in there, the four expert in their reports, I don't see them talk about contamination at all, or I don't remember any of the direct evidence to show that there is contamination. So I didn't go ahead to address that.
So if there's no evidence to show that they have contamination in the report of the plaintiffs' expert, I really don't. You ask me about opinion back then this and that. Because my opinion was -- was trying to address what was offered from the plaintiff experts.
If they have no trouble, they have no issue with it, I don't see why I should be here to address that.
And at the end, the only evidence I've been aware is this root cause that ZHP did. They actually test their DMF, and it showed clearly with the data. So I'd like to see what exactly data we actually have on our table.
The data was the DMF they tested was -- I think the dimethylamine was like 10 ppm, give or take. I might be wrong on the exact

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number. And the dimethylamine was probably less than 5 ppm. That's the data, right?

So if we have the data and your expert didn't raise any evidence to support that, I just don't know what you expect from me.

Q. I expect you to actually just answer my questions and not give me a lecture, honestly.

A. I'm sorry. I really don't intend to give anybody lecture.

Q. Because with all due respect, this is your first time as an expert, and there may be things that you're not aware of about your role or what would be expected of you.

A. I will learn over time.

Q. You will, I'm sure. Just like we all do.

Did you see any Certificate of Analysis in any document you saw from the suppliers of the DMF to ZHP? Was that in any of the documents you were provided? Did you see that?

A. I thought -- you called a lecture. I just I --

Q. Just say yes or no or "I don't

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know." I mean, why -- why do I need a long speech?

Did you see a Certificate of Analysis for the DMF from the manufacturer, supplier, or not? I just want to know if you saw one.

MR. BERNARDO: Dr. Xue, if you don't know or you don't recall, just tell Mr. Slater you don't recall having seen them.

THE WITNESS: I don't -- I don't recall seeing one.

BY MR. SLATER:

Q. If you saw the Certificate of Analysis for the DMF and it showed that there was -- that there was DMA in the DMF, that would be important, wouldn't it?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: You are speculating, right? So you say if I saw on the certificate that provide me DMF contains -- I don't remember the number -- that amount of DMA, right?

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And that definitely is a factor that will take the -- the challenge or that the puzzle to a different level. Because now you know there's this much DMF -- DMA actually present in my solution.

BY MR. SLATER:

Q. When you did your analysis of what the chemists at ZHP should have done in your report --

A. Uh-huh.

Q. -- were you evaluating whether or not they should have been aware of potential reactions and potential creation of impurities in their process?

A. I like your word "potential" because that's our -- for myself in my career, that's something really we address all the time as well.

So as a scientist, we -- we do that all the time, right? So potential side reactions is definitely something we talk on daily basis. Every project almost every reaction, unfortunately, you always have something.

So as a chemist, as you asking,

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right? So, yes, I think that's very important to actually understand or trying to figure out, foresee things.

But everything, unfortunately, has a scope, right? So you have a project. You have your idea. You have your thought based on what you learn was made available to you. You can't -- you can't actually try to foresee or predict what -- what potential things out there I'm trying to duck or get away from.

But that's -- that's the reality, right? So what's -- what's available big, bit question, right? So you need to -- you need to really try your best to optimize the scope that you can be foresee things. But, unfortunately, as scientists, we never do. We never do, especially for chemistry, right?

So people say chemistry is experiment. Unless you have the experiment to show, okay, this condition that will happen, right? So it's hard. Although you can learn through textbook, through -- through your advisor and things, but there's really just those potentials you cannot always predicting.

So you try the hardest try to -- to actually help yourself, but, unfortunately, that's not means you can -- you can foresee everything out there.

Q. Are you aware of whether or not ZHP was required to ensure that there were no genotoxic impurities in the valsartan it was manufacturing?

MR. BERNARDO: Object to the form of the question.

THE WITNESS: Well, as I said --

MR. BERNARDO: Wait. Dr. Xue, hold on. Let me get my objection.

Object to the form of the question. Beyond the scope of his expert opinion. Compound.

Go on. You can answer, Dr. Xue.

THE WITNESS: Well, the Internet was not very stable.

But I'm not a regulatory scientist. About these requirement or regulatory science-related questions, I



really not sure whether I'm the right person to ask.

MR. BERNARDO: And, Adam, I'll repeat. When we're at a breaking point. We've been going an hour and a half.

MR. SLATER: We can do it right now.

MR. BERNARDO: Okay. Great.

THE VIDEOGRAPHER: Going right now.

MR. BERNARDO: I think the logical time for a lunch break.

MR. SLATER: Fine. How long do you want?

MR. BERNARDO: Dr. Xue, how long --

THE VIDEOGRAPHER: The time is 12:54 p.m. We're off the record.

(Whereupon, at 12:54 p.m., a luncheon recess was taken.)



AFTERNOON SESSION

(1:33 p.m.)

FENGTIAN XUE, PHD

called for continued examination and, having been previously duly sworn, was examined and testified further as follows:

EXAMINATION (CONTINUED).

THE VIDEOGRAPHER: Time right now is 1:33 p.m. We're back on the record.

MR. SLATER: Okay. Let's put up as Exhibit -- is it 8 that we're up to?

We're going to put up an article as Exhibit 8. Let's get it up there.

(Document marked for identification as Xue Exhibit 8.)

BY MR. SLATER:

Q. Now, Exhibit 8 is an article titled "Dimethylformamide: Purification Tests For Purity and Physical Properties" dated in 1977.

Do you see this?

A. Yes, I can see by your reading.



That's correct.

Q. And we saw this on your supplemental list of materials reviewed.

Do you recall reading this?

A. I -- I think so.

Q. And this is published by the International Union of Pure and Applied Chemistry in 1977.

Do you see that?

A. That is correct. 1977.

Q. Let's go -- obviously we don't have -- let's go to page 887, please, and we'll go to the top half of the page.

MR. SLATER: Can you blow that up, please, Chris?

BY MR. SLATER:

Q. And if you go down almost halfway down the page, after the first formula, there's a sentence that starts with the word "Formic acid."

Do you see that?

A. Yes, I do see formic acid.

Q. It says:

"Formic acid and dimethylamine are thus predominant impurities in DMF and determine

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the odor of the impure solvent."
Do you see that?
A. Yes, by reading. That's correct.
Q. You would agree with me that the fact that DMF may contain DMA as an impurity was something that a chemist who was working with DMF in a manufacturing process for a drug product should have known, correct?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: I disagree.
BY MR. SLATER:
Q. Let me ask you this question.
Let's talk about what ZHP did with its processes, the TEA with sodium nitrite quenching and zinc chloride process.
You're familiar with both processes, right?
A. Yes.
Q. And you're familiar with the fact that it was ZHP that developed those processes, correct?
A. The process of TEA with quenching and zinc chloride was -- for manufacture was

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developed by ZHP, but the chemistry part was not developed by ZHP because there are -- these reactions have been out there before they actually used in their projects.
Q. The manufacturing processes that were titled the TEA with -- jeez. Let me start over.
What -- what do you mean by what you just said when you -- when you provided that --
A. Well, like in --
Q. -- explanation at the end? I don't understand.
A. -- my lab -- my lab develop a reaction, I publish this reaction or I patent this reaction. And then you if you own a lab, you can actually use my reaction published to develop your own process. You can use mine.
So ZHP for their TEA process or the zinc chloride process, all these particular reactions in their process was not invented by them or developed by them. They are there before these two processes are -- are established.
They use other people's work and develop their own. They use other people's to

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develop their own.
Q. Did the TEA process with sodium nitrite quenching -- was that something that was in use before ZHP started using it? That integrated process, did that exist before ZHP used it?
A. Maybe I didn't make myself clear.
So the chemistry part are known, but both ZHP -- TEA with quenching process or the zinc chloride process. But for in term of API synthesis using those chemistry, I think ZHP, they actually patent those.
Q. When ZHP created those processes, they knew that they were going to introduce chemicals and solvents and various substances into the process, right?
A. Yes. When they actually develop these process, they knew they're going to use reagents and solvent and patent everything in the process.
Q. And do you agree that responsible chemists under those circumstances would need to understand the potential risks of introducing those various chemicals and substances and

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reactions? Do you agree that they needed to understand the risks of doing that?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: Right. For these particular processes, right, when you have API of valsartan in your mind, you have these organic we call it reaction of scheme.
So those are designed and then they should actually know. Everybody when they actually develop something, they will based on their knowledge need to know what are the risks, and then they will try to avoid those risks.
BY MR. SLATER:
Q. And they had to take into account that what they were manufacturing was going to be placed into a medication that people were going to take and put in their bodies, right?
That was the purpose of what they were manufacturing was to create drugs to put in people's bodies, right?
A. Manufacturer, yes. The ultimate

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goal is definitely to -- to make drugs and people can take.

I don't -- because what was the question? So what's their responsibility about what were you asking?

Q. It was a simple question.

When the -- when they were -- rephrase.

The chemists who were involved in --

A. Uh-huh.

Q. -- these processes had to understand that what they were manufacturing was intended to be placed into pills that were going to go into the human body, correct?

A. Yeah. So the -- the manufacturing chemist, as you mention, right, they -- they -- they should be very clear of the ultimate goal of their work will be eventually become pills for patients.

Q. And you would agree that with regard to the various substances -- well, rephrase.

When ZHP changed -- well, rephrase.

You understand that ZHP had four different processes to manufacture valsartan over

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the course of time. You're aware of that, right?

The Tin Process, the TEA process, the sodium nitrite quenching process, and the zinc chloride process, right?

A. That's -- that's correct.

Q. The original process, the Tin Process, you looked at the chemistry of that process, right?

A. Yes, I did look into the chemistry of the Tin Process.

Q. And based on your review, there were no reactions that are in that process capable of creating a nitrosamine, correct?

A. Right. If you ask me now when I -- when I look at this based on my -- my knowledge now, there's no chance for nitrosamine formation based on my knowledge now. I mean, in the future if we discover, that's -- that's -- that's a different story. But now, no.

Q. And the same would hold true for the TEA process, the first TEA process, before they had sodium nitrite quenching, correct?

A. Yeah, with the scope of the knowledge that I have, there's no -- no -- there's

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no reason to form nitrosamines.

Q. When they developed the TEA with sodium nitrite quenching process, that process has the potential to create nitrosamines, correct?

A. As you asked for now, it's a fact. This process did already produce nitrosamine.

Q. If --

A. So everybody knows now. Sorry.

Q. If there was no sodium nitrite or other pathway to create -- to injecting a nitrosating agent into the process, there would be no risk of creating a nitrosamine, correct?

A. Well, nitrosamine is formed from two parts, right? You have, like you said, a nitrosating agent in different forms that, and then you also have to have a secondary amine there. So these two must be there to form nitrosamine. So if you remove one of the two, then nitrosamine will not formed, at least based on my knowledge.

Q. And with regard to the zinc chloride process, the same would hold true. Without the sodium nitrite that was part of the process, there would be no potential to create a nitrosamine,

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correct?

A. Similar to what I said. You need two parts to form a nitrosamine. If -- if you don't, if you cut two -- one of the two parts, either one of the two, then you will not have a chance, based on what I learned.

Q. In terms of understanding potential risks, when ZHP chose to introduce sodium nitrite into the quenching process, they needed to understand that if that was exposed to a secondary amine, that could create a nitrosamine, correct?

The chemists at least need to have that understanding at the basic level who were creating this process, right?

A. I disagree. I think --

Q. So you disagree. That's fine. I just asked if you agree or disagree. I didn't ask you why.

A. Okay.

Q. Were the chemists who decided to introduce sodium nitrite into the sodium nitrite -- rephrase.

The chemists who determined to introduce sodium nitrite quenching into the TEA

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process, as well as into the zinc chloride process, were they responsible to understand the risks of using sodium nitrite in that process?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: You are asking me if the chemists who introduce sodium nitrite into the quenching process of either the zinc chloride or the TEA with quenching process will be responsible for the formation of nitrosamine. That was your question?

BY MR. SLATER:

Q. No. My question is: When ZHP -- well, rephrase.

When the chemists decided to introduce sodium nitrite to quench the sodium azide, they needed to evaluate the risks of using sodium nitrite in that process.

You would agree that was something they had to assess and evaluate, right?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: So when they

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actually introduce any reagent to a process to any of the reactions, they need to know what they add, right? And also they need to track it down to know where this component ends.

So that -- if that's the question, the question is yes. So you should be able to or you should actually track it down and know where the chemical add, where it is.

BY MR. SLATER:

Q. And they need to research to understand the potential risks of using sodium nitrite in that process. They needed to understand what are the potential risks of introducing this to the process.

That's the responsible thing to do, right?

MR. BERNARDO: Object to the form of the question. Vague. Compound.

THE WITNESS: Well, when -- when we introduce any reagent like sodium nitrite, so you need to know what you want to use this for, right? So that

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want to use as you introduce as a quenching reagent, you want to quench the excess of amount of azide.

And then they want to also have a way to track it down to see where it ends, right, so you will know where whether this sodium nitrite they actually introduce will be enough in the final product of things.

So that's I think something a chemist who actually develop this process should know.

In term of whether they would be aware this sodium nitrite can become a nitrosating reagent, I disagree. I think that's something you're not easily aware.

BY MR. SLATER:

Q. Do you have any understanding of the level of scientific analysis that the people working at ZHP were required to conduct based on the regulations and the standard operating procedures that applied to them?

MR. BERNARDO: Again, object. Dr. Xue is not being offered as a

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regulatory expert.

If you can answer it, go ahead.

THE WITNESS: Yeah, it's out of my expertise. I cannot comment on that.

BY MR. SLATER:

Q. So you don't have an opinion as to the extent of scientific research that was expected of the chemists at ZHP in connection with the development and use of the zinc chloride and sodium nitrite quenching TEA processes?

MR. BERNARDO: Object to the form of the question. Mischaracterizes his prior testimony.

THE WITNESS: I do have opinion on that.

BY MR. SLATER:

Q. Okay. So you do have an opinion as to what extent of scientific research was required of the chemists at ZHP --

A. Well --

Q. -- by as a matter of the regulations and FDA guidances and internal SOPs that applied

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to them?
Do you have an understanding of that and an opinion as an expert?
MR. BERNARDO: Object to the form of the question and the characterization of his prior testimony.
THE WITNESS: I can't comment on regulatory science, but I said I have opinion on ZHP had within their scope of knowledge their -- their task a risk assessment in term of chemistry to actually before they actually make any change.
Because as you said, there -- there are four different processes they do. So each one of the change, they have done multistep analysis for their reactions each one of them to do those analysis.
BY MR. SLATER:
Q. Were the chemists at ZHP obligated to determine whether the changes to the manufacturing processes could introduce genotoxic impurities to those processes?

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MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: So genotoxic impurities itself is a pretty broad concept. So can you be more specific like what we talk about here?
BY MR. SLATER:
Q. Do you have any understanding as to whether or not, or to what extent, ZHP was required to evaluate these manufacturing processes for the potential creation of genotoxic impurities?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: Well, although I'm not -- as I said, I'm not a regulatory science expert, but I know that genotoxic species is very broad topic. It's actually, you know, these toxic definition is also very vague. It depends on what disease you talk about.
Like some of the disease, you know, toxic molecule may not be too bad. Like I do cancer research. Some of the

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DNA modifiers actually are the biggest drug on the market. They treat cancer, right? So those are by some sort of definition can be quantified -- qualified as genotoxic. But they are actually out there for -- for patient treatment, right?
So disease or even -- even the dosage format matters, too. Because some drug at a low dose, they can be helpful for -- for disease.
So like, for instance, if you treat people with, you know, with infections antibiotics, some of the nitrous oxide-released molecules can be -- can be drugs, but when you have a high dose, they are actually can be toxic. They cause cancer sometimes.
So it really depends on who you actually talk about, what the patient you talk about, what disease you talk about, what dose level you talk about.
Yeah. So, again, I'm not a regulatory science scientist. I cannot

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really tell you what are the required -- requirements are for -- for ZHP chemist to actually know about.
BY MR. SLATER:
Q. In the context of the processes to manufacture valsartan -- which is not a cancer drug, right?
A. It's -- it's for high blood pressures.
Q. In the context of the processes that we're talking about, the TEA with sodium nitrite quenching and the zinc chloride process --
A. Right.
Q. -- what level of scientific analysis was required of ZHP in order to investigate the potential for the creation of genotoxic impurities in those processes?
Do you have any understanding of what level of scientific research was required?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: For the level of requirement for scientific research, I didn't read much, but I read the -- the

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FDA's announcement about these particular potential genotoxic compound. They were saying either NDMA from the zinc chloride process or the NDEA from the TEA with quenching process, they are just possible, probable cancer-causing reagent.

I remember FDA also highlight in their announcement that even for the patient with the highest dose of these drugs, valsartan I think is over 300 milligram per -- per day for 4 years of full treatment. Like they were saying, if you have 8,000 something like that patient, you possibly can have one additional patient with cancer. So that's -- that's how small the chance will be.

So, again, I'm not a regulatory science scientist, but I just feel this is not -- well, that's the fact that I read from -- from the FDA website.

BY MR. SLATER:

Q. Thank you but not what I asked you.

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Do you have an opinion as to the level or extent of scientific research that ZHP was required to conduct when it was developing these processes in order to determine whether there was a potential for the creation of genotoxic impurities through these new processes that they created? Yes or no.

A. I don't know the requirement because I'm really not a regulatory scientist. I don't know what the requirement ZHP had -- ZHP has to follow to perform their research.

Q. Let's go within that document to page 890, Exhibit 8. The article on dimethylformamide from the International Union of Pure and Applied Chemistry. Very top it says "Tests For Purity."

Do you see that?

A. Yes.

Can you make it bigger, please? Thank you.

Q. It's too big.

A. No, that's okay. Thank you.

Q. Okay. At the top of page 890, it says "Tests For Purity."

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"Owing to its various modes of degradation (hydrolysis, thermal and photochemical decomposition) the principal impurities found in DMF are: dimethylamine" and then it lists some others.

Do you see that?

A. I do see that.

Q. First of all, you agree with me that degradation of dimethylformamide can be caused by -- by thermal cause, right? That's by temperature, correct?

A. By reading that, that's what they talk about.

Q. Well, you agree that's accurate, right?

A. Where now we all learn that that could actually happen.

Q. Well, this is -- this was published in 1977.

So people knew in 1977 that DMF could be degraded by temperature, right?

A. By reading that, that -- that is what the author said.

Q. It was also known that DMF could be

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degraded by hydrolysis, correct?

A. Yes, by reading, that's also there, too.

Q. That's also a true statement in chemistry, right? That DMF can be degraded by hydrolysis, right?

A. That's the authors -- what the authors wrote there. That's correct.

Q. Do you disagree?

A. Well, as a chemist, I always have to be very specific with the conditions, right? So like hydrolysis is -- it's a type of reactions, right? Thermal or photochemical decomposition also covers a whole spectrum of conditions.

So I -- you know, by saying this it just say you're eventually you're going to die, right? So that -- that is too vague as a condition that is given. Because I'm not against this. What I'm saying is by saying what I'm saying here is really, it doesn't tell me what condition the author is trying to actually describe.

Q. What does hydrolysis mean?

A. Hydrolysis means when you have a

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substance in the presence of water, the water can actually attack the substance so that you can actually form a product from water attacking.

Q. Okay. And you'll agree with me that under certain circumstances -- I don't want to go through a whole dissertation on it -- but under certain circumstances, it's known and was known as of at least 1977 that DMF could be degraded by hydrolysis, correct?

A. Well, that's what the author said. As -- as I just explained to you, hydrolysis is a very broad type of reaction condition. They can be actually happening in acidic or basic or neutral conditions, or having other additives add in there, too. Hydrolysis normally coupled with a specific temperature as well as their concentration.

So, yeah. So this is just describe a very general broad type of reaction. That doesn't tell me what specific condition, you know, it will be used.

So, in other words, by just reading this, I saw, okay, there's these authors claim that potentials. But I won't know, for instance,

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what temperature will cause this or what kind of concentration will cause this or how much acid or base it will require to cause this.

Q. The best way to know if a certain manufacturing process will cause degradation of DMF would be to run a test, right? Run a test under the circumstances under which the process is going to be run and see what happens.

If you really want to know if that process can cause that reaction, you can do a test, right? That's -- that's something that you can do, right?

A. Well --

Q. Yes or no. Can you run a test?

A. You can run a test, but that's under assumption that you know what could happen.

So it's like all research I do is we call it hypothesis-driven, right? So you have a idea. You thought something could happen. Then you go out to establish a chemistry or a reaction or a procedure trying to test that. But that's how you make your steps. You move your chemistry or you make your science forward.

So, you know, it's very, very common

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that you -- you will have a goal. You have established a hypothesis that you reach out to see something that is happening.

But I always say, if I don't know what could happen, and then I would not probably not establish an experiment and try to prove something that I didn't expect.

So I hope I explain this like clear. So you have to first have a goal, and then you design something to achieve the goal.

Q. When it was decided by ZHP to use DMF, if they had done research -- which we know they didn't -- into the possible degradation or impurities of DMF, they would have been able to find literature like what I'm showing you right now to know that under certain circumstances DMF could introduce DMA into a process.

They would have at least known that as a general point if they had done the research, right?

A. If they done the research, they read this paper. If I'm the person at ZHP, I do this. I look at this. I say, oh, under hydrolysis, which means in the presence of water. So that's a

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very general situation. Or you have a thermal or a photo. None of these are actually giving me any direct evidence about what is really required.

This is basically telling me all the environment, right?

Q. Right.

A. So we have moistures are run. We have, you know, you have some sort of temperature run. You always have light in the lab unless you have a dark room.

So these are to me, yes, they are statement, right? They are -- they are published. They are available. ZHP, they do analysis. They definitely have a chance to read this paper. They can actually come to this paragraph to -- to read this statement in particular.

But I put myself at that -- their situation. If I read this, it won't actually help me to understand a lot.

Excuse me. Sorry.

Q. It's okay.

If ZHP wanted to do a thorough risk assessment for the introduction of DMF and to know whether or not DMA would be created or be

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introduced into the process, there were certain tests they could have done, and I showed you in the deviation investigation report they did tests.

Those could have all been done in the beginning if they had chosen to do them, correct?

MR. BERNARDO: Object to the form of the question. Compound. Vague.

THE WITNESS: The situation is, if they know. Like we are discussing now. Yes, they -- they actually have a method as you've shown, right? If they, you know, they can do the test.

But the problem for -- for us is back to 2012 or '13 when they are trying to develop these new processes back then. They don't know that and, you know, the very little information around there -- not saying there's nothing, right? So you shown me multiple documents already.

They are not -- to my opinion, they are not give ZHP the hint that they are potentially have trouble of

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generating dimethylamine. I was just not seeing that myself.

BY MR. SLATER:

Q. Well, I've shown you literature and I could keep showing it to you indicating, number one, that it was known that DMA was a known impurity of commercially sold DMF.

That was something that ZHP could have easily known, right?

A. I disagree.

Q. Okay. You disagree. Okay.

A. This -- even this moment I don't think, right? So average chemist can -- can easily know --

Q. Yeah.

A. -- that there -- there in their -- in their DMF they have DMA.

Q. Is the standard you're applying for your opinions what the average chemist in the world would know, or is the standard what a process chemist working at a drug manufacturer who's creating a process to manufacture a drug that's going to go into the human body, which is a regulated area, is that the standard?

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Which one is it: The general chemist walking down the street or the chemist who's actually developing a drug manufacturing process and making choices as to what chemicals to introduce to that process?

I just want to know. Is it A or B?

A. I cannot speak for that, really. I'm a chemist. I view myself as the expert in organic chemistry, but just now when I speak, I really view I myself as an average chemist.

I myself will not be aware of that. So I don't say I'm much better than the people at ZHP. They need to actually develop a process for drug purpose. I fully respect that. They are -- they are smart. They are high-level chemists.

Excuse me.

But the same time I say myself, if I put myself at that -- their shoes, I won't be able to.

Q. Did you read in evaluating -- rephrase.

When you went through the factual information to form your opinions --

A. Uh-huh.

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Q. -- did you see anywhere where ZHP said that the DMA could have been introduced both through degradation of the DMF or as an impurity of the DMF? Did you see whether -- what ZHP said on that topic?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: As far as I remember, when I reviewed the material to form my opinion, I didn't see ZHP talk about introduction of DMA. Because they just don't even know that.

But as you show me this morning, when they do this call deviation study or the -- the root cause study when they know in their process, unfortunately, this particular compound was formed, they did go back to actually try to figure out what was the cause of how it's actually formed.

BY MR. SLATER:

Q. And when you looked at that analysis, did you see that ZHP concluded that the DMA could have been introduced both as an impurity

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of the DMF and/or as a degradation product of the DMF during the process?

Did you see that in the deviation investigation report? Did you -- I just want to know if you saw that.

A. Off my head, I honestly I cannot say for sure I saw that, but that's what I remember, I can tell you. But if you can put up a document to show me, I'll confirm that. But my -- my --

Q. Sure. Let's go to the deviation investigation report, page 7. Same exhibit, Number 5.

A. Thank you.

Q. That's the report I'm using. Page 7 of 236. Very bottom of the page.

A. So you said the very bottom of the page 11 --

Q. Page 7 of 236.

A. I'm sorry.

Q. The bottom of the page.

A. 7.

Q. And you see it says that:

"Based on the investigation and evaluation of the current Valsartan route of

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synthesis (zinc chloride process), this impurity -- which they're referring to NDMA -- is most likely formed during the 'azide quenching' by nitrous acid of the API manufacturing process."

Do you see that?

A. Yes, I do see that.

Q. "Specifically, DMF, one of the solvents used in Step 4 (Crude) stage, may contain trace amount of dimethylamine as an impurity."

Do you see that?

A. I saw that, too.

Q. Do you know when ZHP first learned that DMF can contain dimethylamine as an impurity?

A. I don't know when they first learned that, but based on what you read just now, I'm reading this paragraph, too. They are saying --

Q. I just asked if you know when they learned that. It's the only question I asked you.

A. I don't know when they learned that specifically.

But I just want to point out they say "may contain trace amounts." So they are actually -- I don't think this paragraph is showing they know for sure what happened. They

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just -- they just threw out some hypothesis there.

Q. Okay. It then says:

"Furthermore, during the tetrazole formation step, dimethylformamide may be susceptible to low level decomposition under high temperature to produce trace amount of dimethylamine either via thermo decomposition or hydrolysis."

Do you see that?

A. I saw that, too.

Q. And do you agree with me that the DMF that was introduced to the zinc chloride process may have contained trace amounts of dimethylamine as an impurity at the time that it was being used for the manufacturing? Do you agree with that?

A. You said may contain that, right?

Q. Yes. Do you agree with that?

A. Yes, it is possible.

Q. And do you also agree that during the tetrazole formation step, the DMF may have decomposed under the temperatures that were applied to it to produce trace amounts of dimethylamine either via thermal decomposition or

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hydrolysis?

Do you agree that's a true statement, also?

A. Again, they are -- they are hypothesizing here, right? They are trying to --

Q. Do you agree with the statement or not?

A. I agree with what they said. That's the two possibilities what can actually cause the formation of dimethylamine.

I don't see any direct evidence to show to support these are the case, though, or either one or both are the case. Or maybe not these two, but a third one. So because they point out these are two may -- maybe, right? So that means there are possibly other ones as well.

Q. If you look at the bottom of page 8 -- go to the bottom of page 8 -- it says:

"Based on the above elucidated root cause, the presence of trace amount of NDMA in the final Valsartan API requires the convergence of the following three factors (hence the 'Three Factors Analysis')."

Did you see what I just read?

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A. Yes, as you read, that's the last paragraph on page 8.
Q. Right.
Before right now, were you aware of the Three Factors Analysis that was applied by ZHP in its root cause investigation?
A. Yes.
Q. Did you talk about the Three Factors Analysis in your report?
I don't remember seeing it. Did you?
It's just a yes-or-no question, Doctor?
A. I didn't mention that in my e-mail -- in my report because again --
Q. That's all I asked. I didn't ask you why. I just asked if it's there or not.
A. No, it's not there.
Q. Let's go to the top of page 9 where the three factors are listed.
Number 1. "Presence of dimethylamine in the manufacturing process, such as its presence in tetrazole formation step."
Do you see that?

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A. I see that sentence.
Q. And you agree that the key is that the diethylamine is present. It doesn't matter how it gets there, whether it was an impurity of the DMF to begin with or whether it was a degradation product from the process.
It doesn't matter how it gets there. It just matters that it can be there, right?
A. For the formation of the NDMA, dimethylamine, as far as we now know as scientists, it's required for the reaction since we know dimethyl -- NDMA is formed during this process. So it's going to be somewhere on the process they have it.
Q. It doesn't matter how it got there. It just matters that it was there, right?
A. Yes.
Q. Number 2. "Presence of nitrous acid in the manufacturing process, such as quenching of azide using sodium nitrite."
That's number 2, right?
A. That is number 2 by reading.
Q. The presence of nitrous acid in this process was well known to the people at ZHP from

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day one because they knew that they were going to put in sodium nitrite and hydrochloric acid and that was going to form nitrous acid, right?
A. Yes, I believe so.
Q. Number 3. "The possibility of direct contact between secondary amines and nitrite in the presence of the target product."
That's number 3, right?
A. That's by reading, that's number 3.
Q. And in the zinc chloride process, we know the NDMA formed when the dimethylamine was contacted by the nitrous acid, right?
A. Well, technically, it's not nitric acid. It's the nitrosonium ion that's formed through multiple steps from nitric acid.
Q. The presence of the nitrous acid was necessary to form the NDMA, correct?
A. For -- for this particular reaction talk about here, it is correct.
But I want to say that nitric acid is not the only reagent that can actually generate nitrosative agent.
Q. There's many potential nitrosative agents in the world, but the one that was in this

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process was nitrous acid, right?
A. No, it's nitrosonium ion. It's not a reagent that's directly from nitric acid. You have -- we have to be clear about that. Because nitric acid is not a nitrosative reagent. It's nitrosonium ion.
Q. The nitrosonium ion, you call that as NO plus in your report, right?
A. I draw it that way, yes.
Q. Could there have been NO+ without the sodium nitrite?
A. For this particular reaction, no.
Q. So the introduction of the sodium nitrite led to the creation of nitrous acid, and then the nitrosonium ion NO+ was created at some point and that combined with the DMA to create NDMA.
Is that your opinion?
A. That's the scheme I draw in the -- in my report.
Q. And let's go now to page 61 of this, 61 of 236.
Looking at the bottom part of the page.

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A. I'm -- can you give me a second? I just get to that page. Thank you.
Yes, I'm -- I'm with you now.
Q. This is part of the root cause analysis for the TEA process with sodium nitrite quenching.
Do you see that?
A. So we talk about that.
Q. Left column it says "TEA process (with sodium nitrite quenching)"?
A. I'm sorry. So you talk about the right column?
Q. Left column.
A. Oh, hold on. I lost it.
Q. It says "TEA process (with sodium nitrite quenching)."
A. Oh, yeah. So the last column said that, yes.
Q. And if you go to the right, it says:
Number 1. "Triethylamine hydrochloride was used as catalyst. Sodium nitrite was used for quenching after reaction."
You see that?
A. Yes, I do see that.

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Q. It says:
Number 2. "No DMF solvent is added in crude step, and no dimethylamine will be degraded."
See that? Do you see what I just read, number 2?
A. So number 2 is reading "No DMF solvent is added in crude step, and no dimethylamine was -- will be degraded."
Q. That's what I just read, correct?
A. By reading, that's correct, but that doesn't make much sense to me, though.
Q. Have you ever seen what I'm showing you right now? Have you ever seen this before?
A. Well, I see -- I read many things.
Q. Doctor, I understand you read a lot of things. I'm asking if you read this.
MR. BERNARDO: He's trying to answer your question. Please stop interrupting him.
THE WITNESS: Yeah.
BY MR. SLATER:
Q. Okay.
A. I possibly did, but I just -- I need

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to read each sentence, right? So just now by reading number 2, I had a puzzle.
Q. Have you ever seen this page before? Do you know?
A. I cannot -- I cannot remember from off my mind -- head, no.
Q. Looking now at page 61 of 236 of this deviation investigation report where they're talking about the TEA process with sodium nitrite quenching, on the right-hand side it says:
"Number 3. "Triethylamine hydrochloride may contain diethylamine and dimethylamine, react with nitrous acid (formed by sodium nitrite and hydrochloric acid) during the next quenching reaction, and NDMA and NDEA may be formed."
Is that an accurate statement as a matter of chemistry?
A. Well --
Q. Do you disagree with ZHP's analysis?
A. In term of chemistry, at the same of what they say, if the TEA hydrochloride contain, right? So there's an assumption. If this catalyst used in this particular process, this

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particular step contain diethylamine and dimethylamine, that's the assumption. If they contain those, they can actually react with nitrous -- nitrous acid, which is formed through the sodium nitrite with hydrochloric acid. That's correct.
Q. Let's go to 52 of 236, please.
Looking at the top of the page, this says in part:
"Based on the investigation and the evaluation of the route of synthesis, NDEA is most likely formed in Step 4 crude stage, where toluene is used as solvent and triethylamine hydrochloric as catalyst for the tetrazole formation."
Do you see what I just read?
A. I think you read it right.
Q. Do you agree with that statement that that's the most likely point in the process when the NDEA was formed?
A. Based on the scheme that the -- these people using, based on my knowledge of chemistry, that is the step where NDEA was formed.
Q. It then says -- rephrase.
This report states:

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"Specifically, triethylamine (TEA) may contain trace amount of diethylamine as an impurity."

Are you aware of that, that an impurity of triethylamine can be diethylamine?

A. Well, I didn't -- I think you didn't read it, the whole sentence. What I'm reading is "Furthermore, triethylamine may be susceptible to low level decomposition" --

Q. I didn't -- I didn't read that sentence because that's not what I asked you about. It's a separate sentence.

I don't understand, Doctor. Can you just stick with what my question, please?

A. Right. But I need to first understand which sentence you are reading because you are --

Q. You didn't understand which sentence I read? I read the sentence. I'll do it again. I'm sorry. Let's -- let's try this again.

It states:

"Specifically, triethylamine (TEA) may contain trace amount of diethylamine as an impurity."

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I want to ask you.

Are you aware that triethylamine may contain a trace amount of diethylamine as an impurity? Are you aware of that?

A. So where this --

Q. Yes or no.

A. Where this sentence is?

Q. It's right in front of your face. I just read it to you. Three lines down, it says:

"Specifically, triethylamine may contain trace amount of diethylamine as an impurity."

Do you see that?

A. In the first paragraph?

Q. Yes.

A. "Specifically, triethylamine may contain trace amount of diethylamine as an impurity."

Yes, I read that. Correct.

Q. Did you know that before I just read it to you that diethylamine can be an impurity of triethylamine?

A. Well, my read is triethylamine may contain trace amount. So these statement are all

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hypothetical, right? So I read those. Honestly, that doesn't mean too much to me because they may contain also means may not contain.

Q. What's your opinion?

Does -- does triethylamine potentially contain trace amounts of diethylamine as an impurity when it's purchased?

A. My con -- my opinion --

Q. Do you have an opinion one way or another on that question?

A. I don't know what ZHP bought, right? I cannot judge whether any impurity, including diethylamine was part of the TEA they bought, right? But what I can say my opinion is, this sentence really doesn't show anything really specific. It says "may contain trace amount of diethylamine." It also mean may not contain.

So I --

Q. That's your reading of this? Okay. That's fine.

A. Yeah.

Q. Now, I'm going to ask you again just so we're clear. We move on.

Do you have an opinion as to whether

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or not the triethylamine that was used by ZHP potentially contained trace amounts of diethylamine as an impurity? Yes or no. Do you have an opinion on that or not?

A. I don't have opinion on that.

Q. This states:

"Furthermore, triethylamine may be susceptible to low level decomposition under certain conditions to produce trace amount of diethylamine."

Do you see the sentence I just read?

A. I did.

Q. Do you have an opinion as to whether or not the triethylamine was susceptible to low level decomposition under certain conditions to produce trace amount of diethylamine?

A. This sentence, again, is very vague. That's like all hypothetic. "May be susceptible to low level." All these words are doesn't really show anything scientifically.

So I think I just say I don't have any opinion on this. Because this is really doesn't show anything that is scientific, right? So it may make susceptible means possibility,

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right? So -- or there is a chance, right? So I don't see why this provide anything that's specific.

Sorry.

Q. Do you see at the bottom of the page. Let's scroll down just a tiny bit.

"Conditions for NDEA formation."

And you see it says:

"The presence of trace amount of NDEA in the final Valsartan drug substance requires the convergence of the following three factors."

Do you see that?

A. You talk about the next bullet, right? Number 3. "Conditions for NDEA formation," right?

Q. Correct.

A. There's a bunch of Chinese and then you read the first. You read the sentence in between that "The presence of trace amount of NDEA in the final Valsartan drug substance requires the convergence of the following three factors."

Yes, I saw that.

Q. And the three factors:

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Number 1. "Presence of diethylamine in the manufacturing process; such as its presence in quenching step."

Do you see that?

A. I do.

Q. It doesn't matter how the diethylamine got there. It just matters that it's there, correct?

A. Well, as we just talk about dimethylamine, right? So based off the knowledge we learn so far and because right now we know NDEA already form, this is a required reagent to get NDEA formation.

Q. Second. "Presence of nitrous acid in the manufacturing process, such as quenching of azide using sodium nitrite."

So that's what they state is the second factor, correct?

A. Right. To -- the same reason. To make the NDEA as a product, you need two reactions. So the second it talk about the formation of the second reaction.

Q. Third it says:

"The possibility of direct contact

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between secondary amines and nitrite in the presence of the target product."

That's the third factor listed, right?

A. If you need to form the NDEA, this is what you have to make the two things together. That -- that just said nothing, but based on the analysis from ZHP, what the potential. They actually did the backward analysis.

If we know now this impurity is formed, what are the required reagent. There are two of them required to form this product, and these two required species must be together.

So that's -- that's what they actually do here.

Q. When they refer to "in the presence of the target product," they're talking about the fact that when the quenching takes place, the target product is still present in the mixture, right?

A. Can I read that sentence one more time? So to understand what the target product is?

"The possibility of direct" --

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(reads document).

Yes. My -- my understanding is the target product talk about the drug molecule.

Q. If ZHP had chosen to extract the target product, the crude valsartan from the mixture before quenching, then the product would not have been contaminated with the nitrosamines in either process, right?

A. So if I understand what you describe is, you are saying if -- if ZHP decide to do the extraction before you add the nitrite, right? That's what you described?

Q. Correct.

A. If that's the case, no, you won't be able to form. Based on this hypothesis, right? These two other reactions. You need to see each other. If you don't let them see other, you don't -- before you actually purify a compound, then you don't have a chance to form the product. That's correct.

Q. Do you agree --

MR. SLATER: You can take that down, Chris, for now. Thanks.

BY MR. SLATER:

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Q. Do you agree with me -- well, let me ask it differently.
Do you have any understanding as to whether or not ZHP was required to make every feasible technical effort to prevent the formation of genotoxic or carcinogenic compounds during the drug substance synthesis and drug product manufacturing for valsartan?
MR. BERNARDO: Object to the form of the question. Vague. Compound. Argumentative.
Go ahead, Dr. Xue.
THE WITNESS: Can you make the question shorter? Because you have a long question here.
BY MR. SLATER:
Q. Was ZHP required to make every feasible technical effort to prevent the formation of genotoxic or carcinogenic compounds during the manufacture of valsartan?
MR. BERNARDO: Object to the form of the question. Also, beyond the scope of his report and area of expertise.

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THE WITNESS: I really hope I can, but I honestly I'm not a regulatory scientist. The requirement from FDA or genotoxicity requirement, all these things I'm not familiar with.
BY MR. SLATER:
Q. From the perspective of organic chemistry, if an organic chemist who was involved with these processes at ZHP was required to make every feasible technical effort to prevent the formation of genotoxic or carcinogenic compounds as part of these processes, you would agree it would have been feasible for them to do scientific research, right?
MR. BERNARDO: Object to the form of the question. Vague. Calls for speculation.
THE WITNESS: So I'm not quite clear what compound you talk about. Because genotoxic compound I don't know. I don't have a full list. I assume there's hundreds, if not thousands, of them.
BY MR. SLATER:

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Q. NDMA and NDEA. Those are genotoxic compounds, right?
A. Yes, NDMA and NDEA they are.
Q. So if ZHP was required to make every feasible technical effort to prevent the formation of genotoxic or carcinogenic compounds such as NDMA or NDEA, one of the things that they could have done was to do scientific research, correct?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. I'm just asking. Could they -- could they have done scientific research into that subject?
A. I think the question is, it's very vague because, as I mention just now, the genotoxic or carcinogenic compound is very broad concept. They are also related to the disease and also dose and time. All these things. So it's hard to -- for ZHP to decide what is the scope they have to control.
Although I'm not a regulatory scientist, I'm trying to answer here.
Yes, I put myself at the situation

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to do research or to develop a drug. If you ask me what I need to -- I absolutely need to, I want to do everything that I can to control everything to the best of what I can.
But what is the scope that I need to be aware of, right? So that's the question. If I don't know in my process of NDEA, NDMA, or any other nitrosamine or any compound, right? That is -- that is on the -- on the warning table or on the genotoxic or carcinogenic list, I don't think it's reasonable for -- for anybody to be required to just go out to test everything on the list.
I don't -- I'm not, again, develop a drug past FDA yet, but I know in my lab, we -- we pretty much try to learn based on the knowledge or science available to us and develop our risk assessment.
If something happened, we go back and do those root cause unless trying to fix the -- the reaction so we don't -- we don't -- we don't have this issue anymore. So that's the practice.
I really don't think it's -- it's -- it's reasonable to require a company when they --

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they really don't -- they don't know what -- what is -- like you said, what -- what is the scope. What -- what -- what are the things on the radar they have to pay attention. If you don't know, how can I design something to avoid that?

Q. One of the things they knew was what chemicals and solvents they were introducing into the process, right?

A. I --

Q. It's a yes-or-no question.

Did they know what --

A. For that I agree. They know what they use and they know --

Q. Doctor, I asked a very simple question.

Did the people at ZHP know what chemicals and substances they introduced into the manufacturing processes?

A. They do know and I think --

Q. So the answer is, yes, they knew?

MR. BERNARDO: Let -- let him finish his answer.

MR. SLATER: Well, maybe you could ask your expert when I ask him such

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a simple question, just answer it and not go on to a speech.

MR. BERNARDO: He's qualifying his answer, which he's permitted to do, and you're jumping on top of his question. Let him just finish.

THE WITNESS: Well, I -- yeah, I'm sorry if I went long.

But you asked me whether ZHP knows what they put in their reaction vessel, my answer is, yes, they know.

But you will ask me whether they should know every single thing about every single reaction of everything they add into their reaction vessel, that kind of requirement with my training as a scientist, I think that's a little too much.

Because science is growing, right? Evolving, right? So we know certain compound have this character. That's our current knowledge. Next year or next decade that knowledge might expand, right?

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So you just ask me whether ZHP know what they use in there. My answer is, yes. But -- but whether they will know what's -- what's going to be available next decade about this compound, I will say, no, they probably don't know at this moment.

BY MR. SLATER:

Q. Simple question.

Did ZHP know what chemicals and substances were used in its manufacturing processes for valsartan? Yes or no.

A. They know.

MR. BERNARDO: Object to the question.

THE WITNESS: I'm sorry.

MR. BERNARDO: Object to the form of the question asked and go on.

THE WITNESS: My answer is, yes, they know based on the time and the knowledge around them.

BY MR. SLATER:

Q. Were the chemists and the people at ZHP responsible to know that certain structural

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groups, including N-nitroso-compounds such as NDMA and NDEA, were considered to have extremely high carcinogenic potency and that they were excluded from the threshold approach --

MR. BERNARDO: Objection.

BY MR. SLATER:

Q. -- about evaluation of impurities in drug substances?

MR. BERNARDO: Object to the form of the question. Assumes facts.

BY MR. SLATER:

Q. Do you know whether they were supposed to know that or not?

MR. BERNARDO: Object to the form of the question. Assumes facts. Compound. Vague.

Go on, Dr. Xue.

BY MR. SLATER:

Q. It's a yes or no. Do you know whether they were supposed to know that or not?

A. Well, in your question, you describe NDMA and NDEA as extremely toxic compound. For that I disagree because they are DNA modifiers. There are publications document about these

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compounds to show they are potential or probable -- probable cancer-causing -- causing reagent, right?

So even FDA, they are not super clear whether these are direct -- there is direct evidence to show these particular compounds are actually the direct cause of cancers.

So I don't think it's right at this moment we characterize them as extremely toxic cancer-causing compounds.

MR. SLATER: Let's go to the FDA Guidance for Industry from December 2008. I guess that will be Exhibit 9.

MR. BERNARDO: And, Adam, when you're at a point to break, we've been going about an hour and 10 minutes and I'd appreciate.

MR. SLATER: Well, I'm going to ask a couple more questions about this and then we can break.

MR. BERNARDO: All right.

(Document marked for identification as Xue Exhibit 9.)

BY MR. SLATER:

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Q. This is Exhibit 9. The FDA's Guidance for Industry. "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" December 2008.

Have you ever seen this document before?

A. I don't remember it particularly.

Q. Let's go to page 8. Top paragraph. Blow it up a tiny bit. Okay. Perfect.

At the top of page 8, the last sentence of the carryover paragraph says:

"However, there are some compounds containing certain structural groups" and then in parentheses "aflatoxin-like-, N-nitroso-, and azoxy-structures) that have extremely high carcinogenic potency and are excluded from the threshold approach."

Do you see what I just read?

A. I saw what you just read.

Q. Did you know that before I just showed that to you?

A. I don't remember reading the exact same sentence, but I can see it now.

Q. Do you have an opinion as to whether

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or not ZHP needed to be vigilant to ensure that if there were any such compounds as I just read in that sentence produced as part of their manufacturing process for valsartan that they needed to identify them?

A. So that sentence you were just reading, right, if I want to repeat what you just read, there are some compound containing certain chemical structures, structure groups.

So nitrosamine, as here it says nitroso compound, that's what we discuss here, right? It's -- it's a group of compound which contains infinitive number of nitroso compound, right? So that's like everything has a nitroso group is called a nitroso compound.

Here you talk about there are evidence to show some compound containing this. I really don't think we can actually just say every nitroso compound here. Okay? That --

Q. Do you disagree with the FDA guidance?

A. I disagree with what you interpret -- interpret just now. I strongly disagree.

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Because, again, as I wrote in my report it's clear as a science -- as a scientist, right? It's very clear to me when you actually generalize any statement like this, you see nitroso compound it's highly, extremely toxic. That fundamentally is just not correct.

Because if you know, right, for any nitroso compound to be -- to become a potential DNA alkylator, a DNA modifier, you have to undergo a process which include a type of enzyme called P450, right?

That enzyme has to take the substrate into its active site and every enzyme's active site is very unique. It's not like everything you can take get to the active site.

So there are very specific nitroso compound that can be actually take into the active site, and that can potentially. Even if you get into the active site, it doesn't mean it can be turned into an alkylating agent.

So it's really not fair to say a nitroso compound because it's a nitroso compound so it must be able to be turned into a DNA alkylating agent.

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Q. I didn't ask you that. You know, what, Doctor? I didn't ask you that.
In fact, you're not a general causation expert in this case, and with all due respect, I don't need to hear from you general causation testimony. That's not what I asked you. Okay? So I'd appreciate not being given a speech about whether you think that these substances are dangerous or not or anything like that.
I'm reading from an FDA guidance and asked you a different question which, with all due respect, you didn't answer.
So I'm going -- I'm going to try it again.
Do you have any opinion as to the level of scientific research and analysis ZHP needed to do to make sure that they identified any N-nitroso-compounds that were created during the manufacture of valsartan?
Yes or no. Do you have an opinion as to level of research that they should have done?
MR. BERNARDO: Object to the form of the question and the commentary

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before, particularly in light of the rephrasing of the question now.
MR. SLATER: You know what? I'm going to withdraw the question. I'm going to ask the court reporter to please read back the question I asked before that massive long question -- that long answer that the witness just gave.
Because you're right. I didn't rephrase it exactly the same way. So let's go back to the question that wasn't answered the first time.
(The reporter read the record on page 224 lines 20-21.)
MR. SLATER: No, it was before that.
THE WITNESS: I said I disagree with that because --
MR. SLATER: Please, Doctor. We're not asking you to say anything right now.
MR. BERNARDO: Please don't raise your voice at the witness.
MR. SLATER: I'm sorry, but

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you know what? If you were in my shoes, you'd be just as frustrated.
MR. BERNARDO: I've been in your shoes many times and I don't raise my voice to the witness.
(The reporter read the record on page 223 line 24 through page 224 line 5.)
MR. BERNARDO: Object to the form of the question on the same ground. Asked and answered, particularly in light of the phraseology of that question and the statements in the document.
BY MR. SLATER:
Q. It's a yes-or-no question. Do you have an opinion or not?
A. I do have opinion. I said --
Q. Okay.
A. -- the way you --
Q. I didn't ask you what the opinion was. I asked if you had an opinion.
A. I do.
Q. Okay. Do you -- is it your opinion that ZHP had to be vigilant to make sure they

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identified any nitrosamines that were formed by the processes, or is it your opinion they did not need to be vigilant to try to identify nitrosamines formed by the processes?
A. They do not --
MR. BERNARDO: Object to the question.
THE WITNESS: -- because they don't -- I'm sorry.
MR. BERNARDO: Object to the form of the question. Vague.
Go on.
THE WITNESS: My opinion is they do not because really they have no reason to do any study.
This statement, as I mentioned, you use this statement from FDA, but you interpret this statement totally wrong.
BY MR. SLATER:
Q. There was literature available -- and you said it in your report -- it was documented that sodium nitrite applied to a secondary amine could create NDMA or NDEA,

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correct? That was literature that was available to ZHP, right?

A. My opinion for that is, it's for the secondary amine to react with nitrosonium ion, It's a documented reaction that is not common as the expert of the plaintiffs claim every average chemist should actually know that.

Q. It was a documented reaction such that if the chemists at ZHP had done scientific research, they would have been able to find that reaction documented in the literature, correct?

A. I disagree.

Q. You're saying it's impossible for them to find that in the literature that you told me it's documented in?

MR. BERNARDO: Object to the form of the question. The characterization of his answer, and the not allowing him to finish his answer.

THE WITNESS: I said that my opinion for this on this topic is very clear.

Yes, the reaction for secondary amine to react with nitrosonium

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ion to form NDMA is documented, but it's not as common as the expert on the plaintiff side claim.

And for why I said it's rare, because the reaction require a reagent that's dimethylamine, which is not -- ZHP didn't aware at all their process can actually produce.

So we thought that reactant you cannot possibly expect or foresee the formation of NDMA.

Also, I am here as a scientist. I did research on nitrous oxide. I know nitrosonium ion can actually be reactive. So I'm -- I'm not average here anymore. So I know the other part of the reactivity, right?

Even me, I don't know the presence of dimethylamine. So I really feel these two together that just, as I concluded or I offer my opinion.

I never said there's no way they can figure out this reaction is documented, but the fact that they don't

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have a secondary amine in their reaction as designed, and they don't have enough resource to actually figure that out.

So it's not fair to expect ZHP to kind of foresee this reaction happened to form NDMA.

BY MR. SLATER:

Q. You're not saying it could not have been figured out. You're just saying it would have been hard to figure it out.

Is that what I understand you're saying?

A. What I'm saying is, NDMA formation from dimethylamine and nitrosonium ion is documented but is not common as the expert of the plaintiffs claimed. However, to make it extremely hard is, the two reaction -- one of the two reactant was not there, and ZHP didn't know and not possibly reasonably be expect to know that this dimethylamine can actually -- actually present in their reaction vessel.

That's all what I actually offered as my opinion.

Q. Are you saying it was impossible for

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ZHP to know that DMA was known as one of the primary impurities of DMF?

MR. BERNARDO: Object.

BY MR. SLATER:

Q. Yes or no. Are you saying it was impossible for them to know that?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: As a -- as a scientist, right? So I never say anything that is impossible. I like to see experiment. I like to see data. Everything is supported by data by the science. If there is, you know, there's always be ways.

I don't want to be exclusive like must be, like some of the plaintiffs' experts was claiming everybody should know this. When you see sodium nitrite, you must be doing this.

I just not trained to do that.

BY MR. SLATER:

Q. You're not trained to do that you said? I didn't hear that.

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A. Yeah, I just not trained to be generalize everything will be absolute on anything.
Q. In terms of what the chemists at ZHP -- well, let me ask you this.
Do you have -- you have no understanding of what -- well, rephrase.
You don't know what the ZHP chemists would have found if they did scientific research into the potential formation of nitrosamine impurities -- well, rephrase.
You don't know what the ZHP chemists would have found if they did research the potential impurities of DMF, the potential degradation products of DMF, and the potential impacts of using sodium nitrite in this process, you don't know what they would have found because they never did the research, right?
MR. BERNARDO: Object to the form of the question. Compound. Vague.
Go on.
THE WITNESS: Yeah, I cannot speculate what result if I don't do that. I don't even know if I do something today

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I didn't do yesterday what I would have got. So I cannot speculate.
MR. SLATER: All right. We can take a break now, actually.
MR. BERNARDO: Okay. Thank you.
THE VIDEOGRAPHER: Time right now is 2:54 p.m. We're off the record.
(Recess).
THE VIDEOGRAPHER: Time right now is 3:08 p.m. We're back on the record.
MR. SLATER: Okay. We're going to put up the next exhibit. I think it's Exhibit 10 we're up to.
(Document marked for identification as Xue Exhibit 10.)
BY MR. SLATER:
Q. Looking on the screen, Exhibit 10, this is a document titled "Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API" and it's Version 3 of this report.
Do you see this document?
A. Yes, I do.

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Sorry.
Q. Have you seen it before?
A. Yeah, I don't remember exactly, but I think so.
Q. Let's go to page 7 of 23, please.
The part I want to focus on is the paragraph at the top that says "In addition." It's the second paragraph.
Do you see that?
A. Yes.
Q. At the top of the page it says:
"In addition, as reported in 'Theoretical Investigation of N-nitrosodimethylamine Formation from Nitrosation of Trimethylamine, Journal of Physical Chemistry 2010,' TEA could react with nitrous acid directly to form NDEA without proceeding via the intermediary of DEA. The reaction mechanism is as follows."
Do you see that?
A. Yes, I do see that statement.
Q. Were you aware before right now that ZHP concluded that the nitrous acid could directly nitrosate the trimethylamine to form NDEA?

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A. I read this page before, but I don't think ZHP concluded this. They just cite this reference here to see if that's a possible mechanism.
Q. Do you think these deviation investigation reports are just a series of statements about what might have happened, or do you think they're actually conclusions about what likely occurred?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: They are a bunch of conclusions. They all conclusions, but scientifically to me they are not conclusions. They are speculation. So hypothesis.
I don't think ZHP or anybody here experimentally ever validate whether this scheme showing on the -- the PDF that you showing me is there's any reason this happened.
I don't remember exactly every detail about this paper. This paper published in 2010 was actually as the

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title it's "Theoretical Investigation." There is no experimental evidence to provide whatsoever to support this at all.

I don't want to look down at any theoretical investigation because my lab myself, we do theoretical investigation for many of my projects. So, but we always couple these theories or we call hypothesis with experimental proof.

So this is definitely something you can hypothesize. And by just looking at the drawing here, that make some sense of why they push the arrow here and going there.

And then they can actually conclude with a -- with a hypothesis that the reaction without intermediate can actually theoretically go, but that other than a scientific hypothesis, it doesn't say anything about it.

BY MR. SLATER:

Q. When you pointed out that the title

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is "Theoretical Investigation," that would be, in other words, for someone like me to say this is something that's potential. It's possible, right?

A. You can -- you can say that way. I like to say because, again, I publish paper like this, too, but not exact same topic. I publish papers on theoretical calculation quite a lot. Actually, these are usually -- when I publish, I always have some experimental result there. I use my theory to explain what's going on.

If I only have a theory, that, unfortunately, to me I might be bias here because I never publish this way. When I only have a theory pictured in any publication say this is what potentially can happen, I as a reader always have a big question mark join after that title. Say, yes, there's theory comes up, but let's wait for years to -- to test this.

Q. So there may be a theoretical possibility, a potential for a reaction to occur like this. In order to determine whether or not that is really going to happen, I think what you said is you need to do an experiment. You need to test that -- that potential outcome and see if it

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actually happens when you experiment.

Is that what you're saying?

A. Normally it's not just one experiment because to -- especially to prove a mechanism like these authors trying to do, it's not a trivial thing, right? So I tell you we do these kind of research a lot, right?

So it's a -- it's a -- it's a very well-dedicated desire of a whole series of experiments. Because you cannot, unfortunately, as a chemist, to capture any intermediate or transition state or any of these species on the way. You can only isolate the product to how you actually design an experiment that you can use the product you isolated to prove this arrows that you draw would all be correct.

That's really a big chunk of science in organic chemistry. So that's what I do, but I'll say we probably don't have time to go through the detail. But this is very, very difficult and high-end things. You do need to have a lot of experiment to prove one hypothesis -- hypothetic mechanism.

Q. That's -- what you're talking about

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would also be the process of risk assessment. If you're doing a risk assessment of a manufacturing process, like ZHP was doing, they if -- they recognize something could potentially occur, they would need to do experiments and multiple tests to find out what's really happening.

Is that what you're saying?

A. I agree with you and not agree. Because we -- I remember before the break, we kind of discuss about this, right?

So as a scientist, you're going to know what is your hypothesis. When I know my hypothesis -- like these people, these authors, like my lab we do, too, right? We have a theory. We set it up and then we design experiment toward that to prove -- or prove is wrong or right. So it doesn't matter. But we desire experiment to prove.

But that goal or that hypothesis we call is number one important in your work. If we don't know, like you just described for ZHP, right now we learn NDMA and NDEA are there, right?

So, but before we talk about dozen years ago when we don't know. It's really just

for me, as a scientist, I just cannot visualize that.

Q. This article existed in 2010 and was actually written by people in Beijing, China, correct?

A. I honestly don't remember the authors at all. I don't know. I usually don't read their institutions where they publish, but, yeah.

Q. You would agree with me that a thorough scientific search of the literature should have turned up this article because they knew at ZHP they were using triethylamine. They knew that they were going to use tertiary amine.

So there's no reason why they wouldn't have found this article at least, right?

MR. BERNARDO: Object to the form of the question. Calls for speculation. Vague.

THE WITNESS: I'm not at ZHP. I really cannot. I hope I can answer, right?

So if I -- I just be myself, right? I tell you if I'm in their shoes



what I will do, right? So this is what I will do if I do a search.

I found this paper. In the title, they do theoretical investigation. I will quickly just scan through the article.

If -- again, this is just me. I'm not saying I'm the best, but if I see there's no proof of this theory, I skip it. That's me.

BY MR. SLATER:

Q. We know that when ZHP read the article -- well, rephrase.

We know that when ZHP described the article in this report, they concluded based on this article that TEA could react with nitrous acid directly to form NDEA without proceeding via the intermediacy of DEA.

That's what it says in the report in front of us, correct?

MR. BERNARDO: Object to the form of the question and the characterization.

BY MR. SLATER:



Q. That's the words on the page, right? That's what the words on the page say?

A. That are the words on the page that you were reading correctly, too. But as I said --

Q. I only asked you if that's what it says.

A. Okay. Those are the words by reading from the document to describe the scheme that they draw as a potential of mechanism.

Q. If ZHP had seen this article back when they were developing the TEA process with sodium nitrite quenching and when they were actually using it, if they wanted to test to see whether or not the process was yielding NDEA, they could have tested and they could have looked for NDEA to see if it was being formed. They could have done that if they had chosen to.

That was something that was technologically feasible, correct? If they wanted to, they could have done that, right?

I'm not asking you whether they needed to or not.

I'm asking you: If they chose to do a test to see if there was NDEA, they could have



done that and determined whether there was NDEA, right?

A. Well, I really here I thought -- if this is me, I did a search, very thorough search. I found this paper reading theoretical investigation. I show this proposal scheme, and then there's no evidence.

Honestly, this is something -- I don't want to look down to anybody's work, but this is just, you know, things you draw can make sense, right? Like in organic chemistry.

I teach organic chemistry. I teach high-level organic chemistry. Things like this, as I said, I don't want to be, you know, disrespectful for other people's work, but I will say I will just skip. I won't take it too seriously. That's me.

And I think -- I think what ZHP using, if I read it correctly, is when they found, right? They found, okay, I have this issue now. Let's go back to -- to see what are the possibilities. That's what they propose, one of the possibilities.

Q. If ZHP had wanted to test to see if

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NDEA was being formed in the TEA with sodium nitrite quenching process, it would have been technologically feasible to do that.

The equipment existed to be able to look for NDEA, right? They could have done that if they wanted to, correct?

A. If -- yeah, if the hypothesis is up there, I'm looking for NDEA the method. I don't know whether the method is established, but like you said, the technology, the treatment of should be available.

Q. For example, LC-MS or GC-MS you can look for NDMA with that and that's the type of technology used to look for NDEA and NDMA, right?

MR. BERNARDO: Object to the form of the question. Compound.

THE WITNESS: I disagree because --

BY MR. SLATER:

Q. Wait. All right.

You disagree that you use mass spectrometry to look for NDEA and NDMA?

A. Well, I disagree because there are methods available not just, right? So if you say

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if GC-MS is a potential that I will use, I will say, yes, I will definitely consider GC-MS as a potential to do the analysis. I'm not saying GC-MS is not a potential.

What I'm saying is, you cannot just say, okay, so automatically when you have this potential issue, if you already identified this is some impurity, what is the best way? So, you know, I cannot say GC-MS is the best way. You have to look around to see what is out there, right?

So I'm developing valsartan. What about other companies do also valsartan? Are they -- what they use. So if I don't -- if I don't have any test, right, so I probably look around and see what everybody else does, right?

So I will. That's my practice, right? So I don't want to get myself inventing something which is not like everybody else does.

Q. Just to be clear --

A. Uh-huh.

Q. -- GC-MS and LC-MS technology existed in 2010, 2011, all the way through. That was technologic -- that was technology that was

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available, right?

A. I believe so because I personally used them.

Q. Right.

And that was the technology that one could use to look for NDMA and NDEA if you -- if you wanted to in a substance.

That's the technology -- two technologies that you can use for that purpose, right?

A. Yes. If you have the compound, you can always choose the available technologies, GC-MS, LC-MS. As I said, I use LC and GC both. LC is more feasible for my type of research. Yeah.

Q. And did you see the documents showing that ZHP actually was using mass spectrometry technology throughout this time?

They were using it going back to at least 2009 going through the 2010s up through the time that this was disclosed in 2018.

You've seen some of those documents, right?

MR. BERNARDO: Object to the

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form of the question.

THE WITNESS: There -- there is a lot of documents I saw, and I did remember a lot of document with GC or LC. I believe I saw ZHP used mass spec as their detector to do some experiments.

BY MR. SLATER:

Q. And let's go -- let's go to the next page if we could, page 8 of 23. At the top.

Now, continuing with this deviation investigation report, it says:

"Based on the above report and research paper, since TEA, hydrochloride, sodium azide and sodium nitrite were also used in Valsartan (TEA process), NDEA in Valsartan (TEA process) could not only be formed by reaction of DEA and nitrous acid, but also by reaction of TEA with nitrous acid directly, the updated 'Three Factor Analysis' for Valsartan (TEA process) is as follows."

Did you see what I just read?

A. I saw that first paragraph you just read. I think you read it correct, too.

Q. And you see they revised their Three

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Factor Analysis, which we talked about earlier in the deposition. So now number 1 is "Use of TEA hydrochloride in the process."

Do you see that?

A. I saw that.

Q. And then the second and third.

Number 2 is "Use of sodium nitrite in the process of quenching."

And then the third factor is "Quenching takes place in the presence of target product and DEA/TEA."

Do you see that?

A. Yes, I do see both of them.

Q. So ZHP concluded that the creation of NDEA in the sodium nitrite with -- in the sodium nitrite quenching -- let me rephrase. I got it backwards.

So you now see that ZHP concluded that the creation of NDEA with the TEA with sodium nitrite quenching process could occur just through direct nitrosation of the TEA itself, and that's what they documented here in their report.

You see that now, correct?

It's what I just showed you. That's

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the words on the page, correct?

A. By reading, that's what they were hypothesizing. I won't say this is conclusion, though.

Q. You agree it's possible that that happened, right?

A. I don't agree.

Q. Okay. So you disagree with ZHP on this point?

A. No, I not disagree with ZHP. The paper they publish is really against my -- my -- my knowledge. I -- I really cannot take that scheme and then -- ZHP they may -- they may agree, but I don't agree with that science at all.

Q. Did you do anything in your analysis as an expert to prove or disprove what ZHP stated on this page that I just read to you?

A. I did a search myself from literature to see the reaction between tertiary amines like TEA, for instance, is one simple tertiary amine with nitrosative reagents like nitrosonium ions, for instance.

I didn't see any simple -- any single example to show that without a complicated

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mechanism TEA could actually form through direct reaction to get you NDEA experimentally showing with a condition that ZHP been using for their TEA process with quenching.

So my own opinion for that particular reaction is, before ZHP and Novartis and Solco, they as a team figured this out through a bunch of teamwork, nobody ever know this reaction under the condition that ZHP was performing can actually take place.

Q. And as we discussed, if the chemists at ZHP had come across the literature we just talked about and this concept of nitrosating a tertiary amine, the best way that they could have answered the question of whether this could occur in that manufacturing process would have been to test to see if it was happening.

That would have been the best way to get the definitive answer, right?

A. Well, there are few assumptions we made here. One is ZHP did a search and find that. So if they don't, if they don't realize or hypothesize the potential formation of NDEA, I -- I personally don't see the motivation why they go

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out for a search. Let's put it aside.

If they -- for some reason they had the motivation to do the search, when they see a few papers, including this paper, show up if they happen to see that. I doubt whether they will see it, but if they did like they eventually found it, as I said, as me as a chemist, I read the paper. I will not take it, you know, this there's no evidence or experimental evidence at all happen. I won't do anything for them.

So those two -- those two levels, I really just don't see ZHP has a reasonable reason to actually test NDEA in there.

Q. You referred to what you would do as a chemist.

Do you have any understanding of what the chemists who are working on a process that's to manufacture massive quantities of this substance to be sold around the world to be ingested by humans, do you have an understanding of what their obligation was and what level of scientific analysis they were required to do? Just asking the question. Do you know?

A. I --

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MR. BERNARDO: Object to the question. Asked and answered.

Go on.

THE WITNESS: Yeah, I definitely aware the difference of myself and the people who involved in master production of APIs.

But I will say the principle that we use for research is the same, and I also want to point out that the database that I use for literature search is not just for academic researchers.

Where what I found as a reference is actually available to all the industry people, all the academic people, or actually for you, too. If you go there, right? So that's the same.

So I'm -- what I found with this topic, TEA process with quenching, is that there's almost nothing reported about this project -- about this topic, right?

I mention that in my report, right? So you probably -- I do research

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a lot, but you probably don't, right? You go off other business.

But a common reaction if I see a really average chemist that know this reaction or of people in the industry who know this reaction well, it's well known like the expert of the plaintiff they claim, usually if you search for those reaction, you got thousands, tens of thousands hits.

This particular reaction, TEA react with whatsoever condition to form NDEA. I mean, talk about any, any mechanism, right?

So I did this search. Unfortunately, only can -- can you really feel like with two hands I can count how many hits I got throughout the history. That tells me how little it's known.

That's why I also said for this reaction, my opinion is, nothing is known and this condition, now we learn through this case it's a new condition that ZHP, Novartis, and the other part of

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the company, they together as a team have figured out.

BY MR. SLATER:

Q. Well, actually, Novartis wasn't evaluating the TEA with sodium nitrite quenching process, were they?

A. Well, they are a part of -- what I'm saying is, they throughout back-and-forth communications, all these knowledge were based on that. And then eventually they happen to learn, okay, there is actually NDMA -- sorry -- NDMA or NDEA formation.

I apologize. That's my phone.

Q. Let's go up to the -- let's take this down and go to the next exhibit, which will be --

A. Can I stop to stop that?

Q. Yeah, go ahead. We'll put up the next document while you're doing that.

(Document marked for identification as Xue Exhibit 11.)

BY MR. SLATER:

Q. Let's go to the first page first, and this is Exhibit 11.

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Okay. We've put up on the screen an article that is titled "Nitrosative Dealkylation of Some Symmetrical Tertiary Amines."

Do you see that?

A. I'm sorry. I -- it's 11, right? I'm opening now.

Yes.

Q. And this is an article that was published in 1979. That's what it says up on the left column from when the download was made. Published on January 1, 1979.

A. Okay.

Q. And you can actually go to the end of the article if you don't believe me, and it says received 13th of June 1978 at the end of the article to show you this is 1979 that it's published. Okay?

And if you look at the first paragraph, it talks about the fact that in the very middle of the paragraph or little further down the middle, it says:

"More recently attention has been directed to the public health aspects of the nitrosation of tertiary amines and quaternary

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ammonium compounds."
Do you see that?
A. Yeah, you read it right.
Q. Then the next sentence says:
"It has been shown that a wide variety of tertiary amines can react with nitrite in the pH range of 3 to 6.5 and temperature 37 to 90 degrees to produce nitrosamines in varying yields."
Do you see that?
A. You read it right, too.
Q. So you would agree with me that we've talked about at least a few articles now. There was literature out there available to ZHP that they could have found if they had looked indicating that there was the potential for this reaction and the reactions in the sodium nitrite quenching TEA process to create a nitrosamine.
There was -- that literature was available to show them this is something that could potentially happen under certain circumstances, correct?
A. By reading that paragraph the author wrote, you're reading is definitely correct.

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Q. And, again, if ZHP had done that research, found this literature, if they wanted to know if this was a problem or an issue with their manufacturing process, they could have run straightforward testing to determine whether or not NDEA was being created.
That was something they could have done in response to this literature, right?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: I think there are two things. One is if you by just reading what -- what this literature said, right?
So it says "attention has been directed to the public health aspects of the nitrosation of tertiary amines and quaternary ammonium compounds," and there's really not much.
They also have a few citations there, but these paper, I cannot say I read every single paper of this field. That's not fair. I try to.
So back then in the '70s or

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'80s, there's a big confusion or people -- not confusion.
When they report, they actually put aniline, which is aromatic amino group belong to tertiary amines. So many of examples in these papers they are actually citing actually -- actually having is not truly trialkylamines like TEAs or DMAs or these -- these amines.
Instead they actually talk about anilines. So anilines and real trialkyl tertiary amines are totally different family of compound in terms of their consistency because they have different PKAs.
And that's why, right, so these authors -- that's my second point -- point out. So as the peak range for this reaction is also very critical. They didn't see anything like 1 or 2 or even 2 to 3. They specify saying 3 to 6.5 because that's -- that's -- you see it's just a range of pH, but that's actually not.

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If you read this reference when they talk about the tertiary amine, unfortunately, they are not really tertiary amine. They are aniline analogs. These compound under this range of pH will stay neutral. What I mean -- I probably go through too much technical.
You actually have the nitrogen stay neutral. You maintain the reactivity. That's how you actually. All these connected studies in this paper listed all make sense because you have the activity there.
However, the real tri -- tri -- trialkylamines or tertiary amines like a TEA or DMA, they are not. Their PK is much higher, right?
Under this particular condition, they will not be able to react. That's why people also point out in papers, publications, say, wait, wait, wait.
If you have these particular aniline-like compound they could react

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but they have a real trialkylamine or tertiary amine, they won't react. The range of the pH is critical here.

So if I see this, I would say ZHP that is using for their printing process, which if I remember correctly is 3 or below, right? They -- they use their strong acid to quench it to below 3. So that's -- that's the range 3D printer TEA at least on theory.

I'm not trying to say that at this -- at today we don't form NDEA. Yes, we do have NDEA formed. I said earlier, right, this is a really great example to show that, okay, the teamwork actually identified this particular condition for the -- for this reaction generate NDEA. That's the result.

But, I mean, all these evidence that you show, it doesn't support at all to show that there's a chance for the reaction to take place.

BY MR. SLATER:

Q. When you're looking at these

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articles --

A. Uh-huh.

Q. Well, rephrase.

Do you think that the people at ZHP should have looked at literature like this? If they had actually looked for it and found it and said, well, let's find all the reasons why this article doesn't raise a risk so we don't have to do a test?

Or do you think as a matter of risk assessment they should have said, you know what? These are potential reactions in general. Let's be sure that it's not going to happen with this process so that we're positive that this genotoxic impurity is not being formed.

Wouldn't the better practice be as risk assessment to be conservative and careful and actually run the test based on literature like this?

MR. BERNARDO: Object to the form of the question.

THE WITNESS: Risk assessment is definitely something we need to be very careful, right? So everybody do

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research be very careful with reactions. But as I said, the back-and-forth, the hypothesis is important. What am I facing if I don't know? Like ZHP, they don't know on their radar NDEA for this case in their TEA process with quenching is a potential.

I just don't feel that's reasonable to expect that.

BY MR. SLATER:

Q. Did you -- I'm sorry. I didn't mean to interrupt you.

Do you think that they should have known there was a risk of NDEA before they went and did their literature search? Is that your testimony?

A. My opinion was they don't know, and there's no reason for them to know this reaction can take place. So they didn't take any action, right?

Q. And they didn't do any research because they didn't know.

Is that what you're saying?

Your understanding is because -- let

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me ask it clean.

A. Right.

Q. Your understanding is because they didn't know at the starting point that there was a risk of NDEA or NDMA, they didn't need to do -- go do scientific research to determine whether there was a potential issue?

MR. BERNARDO: Object to the form of the question.

BY MR. SLATER:

Q. Is that what you're telling me?

MR. BERNARDO: Vague. Asked and answered.

THE WITNESS: I really don't know what else I can add, right? So it's --

BY MR. SLATER:

Q. Well, it's a yes-or-no question. Maybe you can say yes or no as to whether I'm right or not in understanding your opinion.

I'm not looking for a speech.

I just want to know yes or no; is that correct?

A. My opinion is they don't know.

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That's -- that's clear. I want to make it very clear. They don't know.

And second, there's almost no reason or there's no reason for them to -- for us to expect them to know back then, right?

So now, of course, in the year 2020 or even 2018 you figure out. After you figure out, it's easy to explain. But before you figure out, back then when they actually developed these, I just don't feel it's fair for anybody to be expected to -- to know everything about the future.

Q. All right. You understand that these scientists and people at ZHP were not just doing theoretical evaluation of the literature.

Well, rephrase.

You understand that what we're talking about here is a risk assessment for a manufacturing process for a drug that's going to then go into the human body.

You understand we're talking about a risk assessment, right? Just yes or no. Do you understand we're talking about --

A. Yes, I do understand we talk about

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risk assessment.

Q. And you understand, as I showed you before, the risk assessment needed to ensure that there were no unidentified genotoxic impurities. You understand that was one of the things they needed to do.

Do you accept that that's part of the purpose of the risk assessment they had to do? Yes or no.

MR. BERNARDO: Object to the form of the question.

THE WITNESS: I don't think -- I don't agree that they have to assess every single potential genotoxic compound because there's -- I don't -- I don't -- I don't know. Tell me if there are people doing that.

BY MR. SLATER:

Q. I didn't ask that. That's not what I asked you. So I'll be clearer.

The risk assessment for these manufacturing processes that are at issue, do you accept that the risk assessments needed to take into account the potential creation of genotoxic

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impurities from the chemicals and substances in that process?

I'm not asking if they had to rule out every genotoxic impurity on earth.

But did they have to at least assess for the risk of genotoxic impurities from the potential reactions of the chemicals that they were mixing together in that process?

Yes or no. Do you have an understanding of whether they were required to do that?

MR. BERNARDO: Object to the form of the question. Asked and answered.

THE WITNESS: I don't --

BY MR. SLATER:

Q. Yes or no.

A. I don't think they're required to do that because although you kind of --

Q. That's fine. You said you don't think so. Okay. Got it.

Looking at the article.

A. Yes.

Q. At the top, there's a little summary

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and in the third line it says:

"The rate of formation of diethylnitrosamine was found to be first order in nitrous acid, triethylamine, and in the hydrogen ion concentration for pH greater than 3.1."

You see that?

A. I'm sorry. I didn't see that. Which paragraph we talk about here?

Q. At the top above, just below the list of authors.

A. Oh, okay. That's the abstract. Okay.

Q. And then it says:

"Rates increased with decreasing amine basicity."

You see that?

A. I saw that, too.

Q. So you -- you were talking about -- before about, in general, about tertiary amines?

A. Yeah.

Q. They're actually talking about triethylamine here.

You see that they actually are talking about triethylamine, right?

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You see the word "triethylamine," right?
A. The word -- yeah. Because just now when you're reading, I didn't read the -- the abstract. I'm reading the abstract. Excuse me.
(Reviews document.)
Yes. Now I read that sentence.
What was your question?
Q. Before you were talking about tertiary amines in general and what this article means.
I just was pointing out you would acknowledge they're talking about in part triethylamine. That's part of the analysis they're doing here.
It's referenced there, correct?
A. Yes, that -- that by reading, that's what they mention here.
Q. And for the chemists at ZHP, if they had come across this or the other similar literature that points out that triethylamine can be nitrosated, as a matter of risk assessment and protecting the health and safety of patients, the reasonable thing to do would be to say, let's just

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test for nitrosamines just to make sure they're not being formed.
That's the prudent thing to do, correct?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: No, that's not. So we said you have to first -- you have to first look for nitrosamine. You know nitrosamine is a potential. That's -- you made the assumption for granted, right?
So we keep going back and forth. They don't have this information in their mind. Nobody ever done this, right? So they don't know this can possibly be -- be happening.
BY MR. SLATER:
Q. I just asked you if -- but you're not -- you're not focusing on my question, with all due respect.
If they had actually done research into the potential side effect -- rephrase.
If they had done the research

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regarding the potential risks with using these various chemicals and found this literature, this article and similar articles in the literature that are out there, and recognized the potential nitrosation of triethylamine, the prudent thing to do would have been just to test for NDEA and NDMA just to make sure it wasn't being formed.
That would be the prudent thing to do with this process that they had just developed to develop drug products to be put in people's bodies, right? That's why they're doing the risk assessment, to protect patient safety, right?
Or don't you have an opinion?
A. (Reviews document.)
Yeah. My opinion is they really don't know this. They -- they --
Q. My question assumed that if they found this literature.
If they actually had done the research they didn't do and found that there's a potential creation of NDEA or NDMA, wouldn't the prudent thing to do in a risk assessment to protect the safety of patients being to do the test to see if it was producing those

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nitrosamines?
Wouldn't that be the prudent thing to do?
A. Your assumption was this paper, right? So I --
Q. Right.
So assume for purposes of my question that they found this or similar literature alerting them to this potential risk.
If they knew that potential risk, you would agree that then they should do tests to see if it happened, right?
A. Well, the condition that here even if they -- like, first of all, I don't think they -- my opinion is solid, okay? I don't want to, you know, change or anything.
This is they don't know there is NDEA formation. You -- you are setting the state saying, okay, they found this paper, while they're reading this paper.
That's -- that's not happening, right? So they cannot find this paper.
Q. I'm allowed to ask you hypothetical questions, Dr. Xue. Okay?

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A. Okay.
Q. We can all agree they did no research. They made no effort to learn about the potential risks associated with using these chemical substances. We already know that.
I'm asking you to assume they actually did do the research and did find literature that indicated that the triethylamine could be nitrosated.
In that event, the prudent thing to do as part of a risk assessment to protect patient safety would be to run a test and see if it was happening here, right?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. Wouldn't that be the smart thing to do?
Wouldn't that have been the smart thing to do because then they never would have had this problem because they would have found the NDEA and this never would have happened?
MR. BERNARDO: Object to the form of the question. Calls for

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speculation. Assumes facts.
THE WITNESS: Yeah. Although you said you are allowed to ask me hypothetical questions, I really -- I cannot answer hypothetical questions.
So you said the stage start there and plus. So I say if you read that condition, they actually talk about here. They clearly say in their first paragraph it's 3 to 6 and a half and that there's a reason. I explain just now why those can actually take place, right?
So and now, yes. So they -- when they talk about the TEA, if we really want to discuss this, I need time to read the whole paper. I don't remember much of the detail of this paper, but -- but I can tell you that by just reading the -- the part, they're talking about the -- the pH value is greater than 3.1. That's their -- but that's their study were performed.
BY MR. SLATER:
Q. So is it your opinion that when the

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chemists at ZHP -- well, rephrase.
If we assume the chemists at ZHP had actually done scientific research and had actually found this article, your -- your understanding of their obligation in doing a risk assessment for potential genotoxic impurities is to look at the article and say, well, it's not describing the exact conditions of our process. So we don't have to worry about it and we don't have to test it.
Is that your understanding of what a reasonable risk assessment is?
MR. BERNARDO: Object to the form of the question. Assumes facts. Argumentative. Calls for speculation.
THE WITNESS: Right. As I said, it's a -- it's a hypothetical question, right? So it's a question that this paper, also the condition here, even this paper describe this is not the same as what they actually use in this piece conditions.
BY MR. SLATER:
Q. I just said that.
A. Right.

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Q. What I asked you is: So you -- is it your opinion that in doing the risk assessment, the chemists should look and say, well, it's not the exact conditions of our process. So we don't have to worry about it and we shouldn't assess and make sure there's no NDMA.
That's what your opinion is?
If you see that there's potential nitrosation, if the article doesn't replicate the conditions of the process, you should just say, okay, nothing to worry about. We don't need to test?
MR. BERNARDO: Same objections.
BY MR. SLATER:
Q. Is that your opinion?
A. (Reviews document.)
Yeah, if I -- as you point out, right? If ZHP, they happen to know this paper and then they read this paper, yeah. As I said, I still find this condition is -- is very different or significantly different because the condition they run, all these tests are different to what actually the quenching process of TEA with

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quenching API process. I won't.
Q. If the ZHP chemists --
A. Uh-huh.
Q. -- were aware in general that the triethylamine could be nitrosated by sodium nitrite, if they knew that in general, the prudent thing to do as part of the risk assessment to protect patient safety would be to do a test to make sure it's not creating a nitrosamine.
That would be the prudent thing to do, wouldn't it be?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: Yeah, it's hypothetic, right? So you, again, say if they know this already, but they don't know.
BY MR. SLATER:
Q. Well, I didn't say "if they know this already."
I said if they knew of the potential for the sodium nitrite to nitrosate the triethylamine.
In general, if they knew it could

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happen under certain circumstances, there would be no reason for them not to do a test to make sure it wasn't happening here, correct?
A. For me, I just don't see. It's like see -- you said if they say if they have the potential. I'm -- like me, I never heard about this reaction in my life before I be involved in this.
If you tell me there's a potential. Every day every reaction has a potential, right? So how can I just because I hypothetically think about some potential?
And if you're going to go back to do a risk assessment on every potential, again I'm running labs. I'm running project. I just don't feel that's reasonable to let my students go into the lab and running, I mean, think about any potential things that can happen. Potential. There is everything has, you know, infinitive potentials.
Q. So you're saying because you wouldn't do that and you wouldn't require that in your lab, you would assume it wouldn't be required for process chemists at ZHP developing a drug for

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mass production that they wouldn't need to do it either?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: I'm not saying that. I say everything as a scientific project, we have a scope. We have based on the knowledge that we learn, we try to test the scope. What are the potentials, right? We know these are possibles.
But you cannot force people to even consider the ones that to them are not possible. I think that's -- that's just not fair anymore.
MR. SLATER: Let's go to another article. Let's to the theoretical investigation article.
Have we shown that already or is this a new exhibit?
Okay. So Exhibit I think it's 12.
(Document marked for identification as Xue Exhibit 12.)
THE WITNESS: Can I go back?

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MR. SLATER: You tell me, Chris. It's 12.
BY MR. SLATER:
Q. So we're now going to put up as Exhibit 12, the "Theoretical Investigation --
A. I'm still.
Q. -- of N-nitrosodimethylamine Formation from Nitrosation of Trimethylamine."
Do you see that?
A. Hold on. I'm still loading.
Q. Okay.
A. Yes, it show up on my screen.
Q. And if you look at this article, which is published in the Journal of Physical Chemistry in 2010 from the American Chemical Society, let's look at the Introduction.
Can you blow it up, please? Perfect.
And in the Introduction, if we go to the second paragraph. It's okay.
The second paragraph says in part, I want to focus on the part that I want to talk about.
In the middle of the paragraph,

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there's a sentence that says "In addition."
It's about five or six lines down.
Do you see that?
"In addition to secondary amines, however, a wide variety of tertiary amines have also been demonstrated to react with nitrous acid to produce N-nitrosamines in aqueous solutions."
Do you see that sentence?
A. Are you talking about the left column?
Q. Yes.
A. Or the right?
Left column. You said the second paragraph?
Q. Yes.
A. Okay. So I'm reading.
Q. In the middle of the second paragraph under the Introduction on the left column, it says:
"In addition to secondary amines, however, a wide variety of tertiary amines have also been demonstrated to react with nitrous acid to produce N-nitrosamines in aqueous solutions."
Do you see that sentence?

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A. Yes, and I will read it.
Q. The creation of NDEA and NDMA in the TEA with sodium nitrite quenching process occurred in aqueous solution, correct?
A. Correct.
Q. This sentence -- well, rephrase.
If the science -- if the chemists -- rephrase.
If the chemists at ZHP had come across this article back when they were developing or using that manufacturing process and had seen that sentence, should that have been alerted them, this is a potential reaction that we should risk assess for to make sure it's not happening?
Would you at least agree with regard to that sentence that would be enough to say, okay, let's do a risk assessment and see if that's actually occurring here? Because if it is, it's not a good thing and we need to make sure it's not happening?
A. Well, there is -- there is a quite a few assumptions, right? You said if they did a literature search, found this article and also if they read the -- the Introduction and find this

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sentence, right?
Q. Yes.
A. Let me see this article.
(Reviews document.)
Yeah. Under those two assumptions, if I really specifically coming to look at this paper, right? Which I don't think they will, these people, too, because, again, there's no motivation for them and this is hypothetical, right?
But let's say if they found this paper and if they read this paper, if I -- I was ZHP chemist, I read this paper again. This is -- I don't know whether this is same paper, but this is a theoretical Investigation of -- of nitrosodimethylamine from which NDMA formation from nitrosation of triethylamine, right?
So this article tells me that, oh, this paper was solely on this simple -- actually structure, that's the simplest tertiary amine is triethylamine. So they do some theoretical investigation on this simple structure of the -- the amines. That -- that -- that's really not relevant to what I'm doing if I'm ZHP.

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And then the next thing I will be caring about if you set the stage like you were talking about, I -- I for some reason I just start to investigate. I found this article. And that's what I'm going to do is I read the -- the title, right? That title is irrelevant, but if I do this, I do scan.
I saw, okay, there is multiple schemes. Talk about this hypothetic schemes that these calculations was done for this particular trimethylamine, which, again, it doesn't relate to anything that ZHP is trying to do.
And then I, more importantly, if I wrote down, right? If I recalculate, these authors, again, didn't do any experiment to show any evidence that what -- whatever they see they actually hypothesize.
Actually, the -- so if I'm ZHP -- like you said, right, I'm not against those. Let's just follow what you set up the stage. Although I don't agree those will happen.
Even if that's the case, if I'm ZHP, I read. I won't pay attention because I won't read the detail about what the, you know, the

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Introduction will talk about because really there are two major facts, right?

So their title has only a sole substrate discussed in the whole paper in the model establishment. Second, there's no evidence from experiment at all to show any evidence any of these theory is correct.

Q. Do you have any idea what the purpose of the risk assessment was that ZHP was supposed to do with regard to these two manufacturing processes that developed nitrosamines? Do you have any idea of what the purpose of that risk assessment was?

A. Yes. From chemistry point of view, they need to see every reagent they use what the -- what the -- what the change will be caused. If they -- if they change any condition in their environment, in -- in their reaction conditions -- like the reagent, the raw material -- they're going -- they're going to check and follow all the intermediate information, the yield and also the impurities. Like they added things they have to track down where they are.

Every solvent they use in any

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process, they have to track it down where they are, how much they have there. So they're going to do this kind of control for every single step on their process. That's my understanding of risk control.

Q. Was the risk assessment supposed to take into consideration whether the reactions could potentially create genotoxic impurities? Was that supposed to be part of the risk assessment as you know?

MR. BERNARDO: Object to the question. Vague. Overly broad.

THE WITNESS: Genotoxic, as I said, right, is such a broad term, right? So you have to be specific. If you only look at the reaction, let's say NDMA formation or NDEA formation, there's still endless infinitive number of potential harmful compound out there, even if you limit to that specific process.

Because you still have multiple reagent, multiple steps, and multiple mixtures at every given

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situation, temperatures and also the volume change as well. So you still have -- have endless compounds to consider.

So as I said, we have to identify the -- the compound you want to test or you want to control. Before that really, you know, I think it's not reasonable to expect people to -- to just know everything about what they do.

BY MR. SLATER:

Q. That wasn't actually my question about knowing everything in the world.

ZHP developed these processes to manufacture pills that they were going to sell commercially to patients to control their blood pressure.

You understand that's why they were developing these processes, right? So they could sell pills that people would buy and take for blood pressure control?

A. Yes.

Q. As part of the risk assessment, I just want to know your opinion. Or if you don't

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have an opinion. I need to know the scope of what your -- your expertise goes to and what you think you can draw opinions on.

Do you have enough of an understanding of the purpose of the risk assessment in terms of protecting against quality or purity issues that could be dangerous to the health of patients in terms of how extensive the risk assessment was supposed to be?

Do you have any understanding of that at all?

MR. BERNARDO: Object to the form of the question. Asked and answered.

THE WITNESS: Yeah, I'm here as an organic chemistry -- chemist. I -- I already explained my -- my understanding about risk assessment from the chemistry point of view of each reaction, each reagent, each solvent they use.

I also comment in my report about what ZHP have known to actually done according to those areas.

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So in term of preparatory, we discuss earlier. I'm not qualified to comment on those.

BY MR. SLATER:

Q. Let's go to page 459 of this article, please.

I want to go to the right-hand column, the bottom right. Just above the last paragraph.

And you can see at the very bottom of the last paragraph on the right-hand column, there's a sentence that says --

(Music)

Looking at the last full paragraph in the right-hand column on page 459 of this 2010 article, it says:

"The nitrosation of secondary amines has already been extensively studied, and the DMA has been confirmed to be easily nitrosated into NDMA in an acidic nitrite solution."

Do you see what I just read?

A. I saw the sentence that you just read.

Q. The nitrosation in the zinc chloride

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process occurred in an acidic nitrite solution, correct?

A. The quenching process, yes.

Q. If ZHP had actually done research and found this article, would you agree with me that this would have been enough to place them on notice that as part of their risk assessment, they should at least test what was being manufactured with the zinc chloride process to rule out NDMA being formed?

A. I disagree with that.

Q. So your opinion is that they could just ignore the potential creation of NDMA, a genotoxic impurity?

MR. BERNARDO: Object to the form of the question.

THE WITNESS: I disagree with -- I disagree with just what you just said because this talk about what you know. There's secondary amine specifically dimethylamine and also nitric acid, right?

So, but the fact is that they don't know if they have dimethylamine or

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DMA in their reaction.

So I think we talk about this multiple times already, but this particular reaction I mention already. My opinion is very clear. It's documented --

BY MR. SLATER:

Q. Okay. Let me ask you.

A. -- it's not common.

Q. Sorry. I didn't mean to interrupt.

A. Can I finish?

Q. Yeah, go ahead.

A. Yeah, but it's not common, okay? And here I think you got confused or I didn't explain myself clear.

It's not this reaction is not -- is not documented. It's documented. But the fact that ZHP, they don't know anywhere in their reaction they can form DMA. Therefore, they don't have a reason to test.

I want to make it clear this time.

Q. Okay. You agree the reaction described in this sentence was documented in the scientific literature before they developed these

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processes, correct?

A. I agree the reaction between DMA or secondary amine, simple secondary amine like DEA, for instance, with nitrosonium ion is documented.

Q. That's all I asked.

A. Right. I agree.

Q. Okay. And your opinion is because ZHP didn't know that there could be DMA in the process, there was no reason for them to be concerned about this nitrosation reaction.

Is that what you were just telling me?

A. It's almost, right? I said, yes, what you said is part of my statement. They don't know this. Therefore, they don't know NDMA formation.

The other is, I also said that for the formation of nitrosonium ion is also something not that common. It's not like when you add sodium nitrite. Everybody knows there is nitrosonium ion. Sodium nitrite doesn't equal to nitrosonium ion.

I never named or -- or described sodium nitrite as a nitrosative reagent. They

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don't know this, right?
So it's -- it's there. I don't say -- I don't say it's not there, right, but it's not like everybody knows that automatically.
Q. If ZHP had known of the potential for DMA to be introduced into the zinc chloride process, in that case, you would agree with me that as part of their risk assessment, it would have been prudent for them to evaluate whether NDMA was being created, right?
A. Well, I won't say they must know that, right? I say this particular reaction you just read me is documented. So it's there. So as people can actually learn it, but there are two parts. One part is the DMA part. They just have no idea about it, right?
So the other part is also not common. It's not like everybody learn general chemistry, go through graduate school. They all know nitrosonium ion equal sodium nitrite. They are not. You use sodium nitrite for multiple reaction as a quenching reagent. I personally never used it, but they are used, right? So I knew that, right?

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So it is not -- we cannot draw a simple equation and say everybody knows that. Yeah, I recall, you know, some of the expert on the plaintiff side said that. I really cannot agree with that.
Q. You would agree that the chemists at ZHP should have known that there was going to be in acidic nitrite solution at the quenching phase, right?
A. Yes, because that's what they used.
Q. And this article says that DMA has been confirmed to be easily nitrosated in NDMA in an acidic nitrite solution.
So if ZHP had been aware of the potential for DMA to be introduced to the zinc chloride process, either as an impurity of the DMF or as a degradation product of DMF, under those circumstances, they would have been on notice as part of their risk assessment of the need to test to determine if NDMA was being formed.
Do I now understand the difference?
MR. BERNARDO: Object to the form of the question. The characterization of his testimony.

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THE WITNESS: Can you please chop your question little shorter? Because I, you know, I'm...
BY MR. SLATER:
Q. Number one, the chemists had to know that they were creating an acidic nitrite solution at the quenching phase, right?
A. Yes, they know that.
Q. Number two, they knew they were using DMF and introducing that to the zinc chloride process, correct?
A. Yes, they knew they used DMF.
Q. If they knew that the DMF could introduce DMA to the zinc chloride process, either as an impurity or as a degradation product, then under those circumstances, they would have been required to take the prudent step of testing to see if NDMA was being formed, correct?
MR. BERNARDO: Object. Object to the form of the question. Vague. Outside the scope of his expertise.
THE WITNESS: Yeah. Well, for the required part I cannot comment too much, but I'll say, right? So my --

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my -- my opinion state clearly. This reaction is a known reaction. It's documented. But it's not common, right?
So both of the substrates are required. I said even those are there, they are not very common people will know. Because sodium nitrite you cannot just draw an equation and say it equals nitrosonium ion.
And for the secondary amine, they don't know, right? So if you say, oh, they already know they have a secondary amine, then they automatically will know this reaction will take place. That's my opinion, right?
So I said, yes, it's documented. This reaction is documented. People knew this. I never say this never published or nobody knows. There are publications on this particular reaction when you have the secondary amine and your nitrosonium ion. But nitrosonium ion, you need to figure out that you have nitrosonium ion.

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And when you have those two together, you still need to have some knowledge about this reaction there to be aware there's reaction take place.

Could there still be multiple stage? A chemist at ZHP has to kind of get together at the same time with the people assumption that they know there DMF contains or degrade to form DMA, which we talked about so many times that they don't know.

BY MR. SLATER:

Q. The whole thought process you just walked through, ZHP never went through that thought process because they never evaluated any of this literature, any of these questions, right?

MR. BERNARDO: Object to the form of the question. Vague.

BY MR. SLATER:

Q. Nothing you've seen, right?

A. Well, I'm -- I'm here --

Q. Doctor, could you just answer my question, please?

ZHP never even considered what you

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just went through. They never went through a thought process of whether or not there was an issue with any of the things you just went through.

It's just something they never thought about, correct?

MR. BERNARDO: Object to the form of the question. Argumentative.

THE WITNESS: Yeah, I cannot speculate other people's thought. I do --

BY MR. SLATER:

Q. Did you see anything indicating that they thought about any of these things?

A. What specific things you talk?

Q. What we just talked through. That whole description you gave of the whole thought process you'd have to go through in evaluating the literature.

You've seen nothing indicating that anyone at ZHP thought about any of those things, right?

A. Well, I'll put it this way. If you ask me in October before I'm involved in this

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case, I have zero --

Q. I'm sorry. That's not what I asked you, and I don't have unlimited time.

A. Right. So you -- you ask me --

Q. What you saw in the records and the documents you read --

A. Uh-huh.

Q. -- you saw in the materials -- new question.

In the materials you reviewed, you saw no indication that anybody at ZHP thought at all about any of the things you talked about in your prior answer in terms of analyzing the literature because they never went that far to actually even look at the literature on this question, right?

MR. BERNARDO: Dr. Xue, I know it's late. Just listen to what Mr. Slater is asking. He's simply asking if you've seen anything in the documents you looked at.

THE WITNESS: I didn't see any documents directly showing that.

MR. SLATER: I'm getting --

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this is probably a good time to take a break.

MR. BERNARDO: Sure.

THE VIDEOGRAPHER: Time right now is 4:21 p.m. We're off the record.

(Recess.)

THE VIDEOGRAPHER: Time right now is 4:36 p.m. We're back on record.

MR. SLATER: Let's put up the deviation investigation report again, Exhibit -- which was Exhibit 5. We'll go to page 155, please.

Just one second before I do this.

Sorry about that.

BY MR. SLATER:

Q. Looking now at page 154 of this deviation investigation report, you can see the middle of the page:

"Test Result of Triethylamine Hydrochloride Samples by Huahai."

You see that?

A. So you talk about the page 155.

Q. I said 154.

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A. Oh, I'm sorry. 154.
You said there is what?
Q. On page 154 in the middle of the page, you'll see it says number 4?
A. Right.
Q. In the middle of the page, it says number 4) "Test Result of Triethylamine Hydrochloride Samples by Huahai."
You see that?
A. Yes. But can you please make it bigger? Thank you.
Q. Okay.
A. That's great.
Q. It then says analytical -- well, rephrase.
It says:
"Analytical method for DEA and DMA and Triethylamine Hydrochloride was developed by Huahai, and the Triethylamine Hydrochloride (from Kente Catalytic materials Co., Ltd) in stock was analyzed. The DMA and DEA results obtained was in Table 4-30 as follows."
You see that table below?
A. You talk about Table 4-30.

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Q. You see it right there in front of you?
A. Yeah, yeah. Okay. Yeah.
Q. First of all, triethylamine hydrochloride, was that used in the TEA with sodium nitrite quenching process?
A. I'm sorry. Your -- your voice was chopped off just now. I just heard the word "process" just now.
Q. Was triethylamine hydrochloride used in the TEA with sodium nitrite quenching process?
A. Yes. Yes.
Q. That's what we've been referring to as triethylamine, right?
A. Yes.
Q. And you can see that they tested for DEA and DMA and they found DEA at 106.3 parts per million.
You see that?
A. I saw that from the table that you show.
Q. Let's go to the next page. Well, actually, let's stop there for a second. I didn't mean to jump that quickly.

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So this is -- rephrase.
This is ZHP confirming that the triethylamine hydrochloride they used in that process contained as an impurity DEA, correct?
MR. BERNARDO: Object to the form of the question. Vague.
THE WITNESS: So what I can read from this table is for this batch number -- I don't need to read the number -- I think they tested for DMA and DEA.
Can we know what LOD -- LOD for limit?
BY MR. SLATER:
Q. Level of detection.
A. Level of detection. Okay.
So I can read that for DMA for whatever method they are using to detect this, it's already below that. So I think the -- the level set for the detection was 45 ppm. And then with DEA, their detect result for this batch was actually 106.3 ppm. That's it.
Q. You would agree with me that ZHP was purchasing triethylamine hydrochloride to use in

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the manufacturing process for valsartan.
You would agree that under those circumstances, ZHP should have known of the potential impurities in that product that they were going to include in their process?
MR. BERNARDO: Object to form of the question. Vague.
BY MR. SLATER:
Q. Or were they allowed to just be ignorant of the impurities that might be introduced into the process and not worry about it?
MR. BERNARDO: Object to the form of the question. Vague. Argumentative.
THE WITNESS: I disagree with what you just said.
BY MR. SLATER:
Q. Okay. You disagree. That's fine.
Let me ask the question differently.
Did ZHP need to know if there was a substance it was going to introduce into its manufacturing process, if that substance had impurities that could be introduced into the

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process? Did they have to know whether or not that could happen?
MR. BERNARDO: Object to the form of the question. Vague.
BY MR. SLATER:
Q. Yes, no, or you have no opinion.
A. I don't think I'm clear about what you asking. You are saying --
Q. I'll be even more clear.
ZHP was using triethylamine hydrochloride to manufacture valsartan, right?
A. That's correct.
Q. As shown here on this deviation investigation report from ZHP, triethylamine hydrochloride has DEA as an impurity in the commercially sold form of that substance.
You see that? That's what this document is showing, right?
MR. BERNARDO: Object to the form of the question. Vague. Characterization of the document.
THE WITNESS: Well, as the document was -- was looking backward from 2018, right? So they knew already at

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this moment when they actually do this analysis where in their -- in their process DMA was formed. And then as you read in the last section there, they also have emphasize the reason why it can happen, right?
So they have the dimethylamine as a reactant. They said somewhere on the process there might be dimethylamine there. They also there, the other part, nitrosonium ion somewhere on this process you can form.
They say when these two together, when they meet in the reaction vessel, they can possibly form. That's what they actually hypothesize.
Here is what they actually show. After they know, okay? In my process in PA with quenching, I saw NDEA. And then I start to track it back to see, okay, what -- whether there's actually, you know, they're basically hunting down where the DEA actually come from.
So what they found and report

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here in their report is that, okay, so the DMA possibly not. If there is, it's definitely below their -- their -- their LOD. And they did find DEA in the -- they come, you know, in the triethylamine sample, the particular batch that they use for this, right?
So I think that this is very logic, right? So I don't see if there are any questions because we -- they did what they did.
BY MR. SLATER:
Q. You literally just told me what the document shows and that is not -- I didn't ask you to explain to me what the document shows. We already went through that. So I'm going to try the question again.
Should ZHP -- well, first of all, let me ask you a foundational question.
A. Sure.
Q. You agree that it's more likely than not that the triethylamine hydrochloride that ZHP used in the TEA with sodium nitrite quenching process contained DEA as an impurity when they

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actually were manufacturing valsartan.
Do you agree? Yes, no, or you have no opinion.
A. I cannot agree because we have to set the -- set the scope, right?
Q. You said, no, you don't agree. Okay.
A. So this -- this table tells us for this particular batch --
Q. I'm not asking about this table, Doctor, and I don't have unlimited time. So I just need you to answer my question.
I'm asking a very straightforward question. Look at me maybe, not at the document maybe we will -- because you're focused on the document. I'm trying to ask you a question not about the document now. Okay?
I'm asking about ZHP when they developed and used the manufacturing process. Okay?
A. Uh-huh. Yes.
Q. That's the time frame.
During that time, in your opinion, did the triethylamine that was utilized contain

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DEA as an impurity already before it was inserted into the manufacturing process?

Either your opinion is yes, it was there, no, it wasn't there, or "I don't have an opinion." That's what I'm asking you.

A. So you ask my opinion whether I believe the TEA catalyst they use in their TEA process with quenching contained an impurity DEA, right? So, but you ask me this question today.

Q. Why don't you just answer the question, please, instead of giving me a speech.

A. I really can't because you ask me today. I, of course, know now based on the data they look backward. They showed, yes, there is, but that doesn't really solve the puzzle, right? So they don't know before and they are not -- they are not looking at that time when they develop for --

Q. Doctor, I'm sorry to interrupt you, but I didn't ask you about what they were looking for. I asked if you had an opinion as to whether it was there.

You just told me, in your opinion, yes, there was DEA in the triethylamine.

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A. I --

Q. I didn't ask you about their research. I asked you one question. I don't have unlimited time. So I need you to just answer the questions I'm asking, please.

A. My answer is, when I look at now, yes, they have the TEA in there. But this is looking backward when they actually figure out. They don't know whether they have it. My -- if you want me a yes or no --

Q. I literally didn't ask you if they knew it was there. I asked what your opinion was as to whether it was there. I don't understand why you persist in giving me speeches about things I'm not asking you, sir.

Let's go to the next page, page 155.

If you go to the middle of the page. Scroll down so we can get the whole middle. Right there, yeah.

Looking at the middle of page 155 of this deviation investigation report from ZHP, it says:

"The results indicate the presence of DEA in Triethylamine Hydrochloride, and DMA was

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less than the level of detection 45 parts per million."

We just looked at that, correct? That's what we just looked at on the prior page?

That's what I just showed you.

A. Yes.

Q. Okay. The next sentence says:

"However, DMA was detected in one batch of Triethylamine Provided by Zhejiang Jianye Chemicals Company Limited. The result is in Table 4-31 as follows."

So you can see they have Triethylamine Test Results down below from a different manufacturer.

Do you see that?

A. You talk about Table 4 dash?

Q. Table 4-31. It's literally there right there on the screen.

A. Okay.

Q. Do you see that they tested that triethylamine that they purchased from this manufacturer, Zhejiang Jianye Chemicals Company Limited, and they gave the results in that table.

You see the results in front of you,

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correct?

A. I do see the table saying for three batches this time, right?

Q. You can see for one batch they actually had 8.2 parts per million of DMA.

You see that?

A. Sorry. What was the LOD for this one?

Q. Level of detection. I don't know. I'm sorry.

Can you just answer the question, please?

My question again is: If you look at the table, it shows the results for testing for DMA and DEA as impurities of the triethylamine from this manufacturer.

You see that in front of you, correct?

A. I do see that number. But can I ask? Because the last LOD was 45. I just curious. Because every experiment has errors, right? So --

Q. Don't know. I only know what the report says. This is all I know is what's right

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in front of you.
A. Yeah, I can read those numbers. I'm with you on those numbers.
Q. So it shows that -- it shows in the first batch, which is the last three digits are 013, it had DMA of 8.2 parts per million and DEA of 85.3 parts per million.
That's documented, right?
A. That is the numbers are correct, but, again, I want to -- if as a scientist --
Q. I'm just asking you if you can see the numbers in front of you.
Is that what the numbers say?
A. Yeah, I can see the numbers.
Q. The second batch 014, it said that no DMA was detected. That's what ND says, not detected. And it had DEA of 28.6 parts per million.
Do you see that?
A. I see the two as you read.
Q. And the third batch 015, for DMA it says ND, not detected, and for DEA 26.1 parts per million.
You see that?

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A. Yes.
Q. Now, my question is this: Based on the fact that there was DEA impurity in the triethylamine -- well, let me ask you this, first of all.
Did you see any indication that anyone at ZHP actually noticed that there was DEA as an impurity of the triethylamine they used in the TEA with sodium nitrite process?
My question is: Of everything you looked at, did anybody at ZHP ever realize that?
That's my first question. Did you see anything to that effect?
A. So you're asking --
Q. That's the question.
A. You're asking the data that we show here in this table --
Q. No, I'm not asking about this data.
I'm asking: Did anybody from ZHP back when they were manufacturing the valsartan with the sodium nitrite with TEA -- rephrase.
Back when ZHP was developing and using the TEA with sodium nitrite quenching process --

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A. Okay.
Q. -- do you see any indication during that time period that anyone at ZHP realized that DEA was an impurity in the triethylamine that they were using? Yes or no.
A. I cannot comment on that. I don't -- I don't -- I don't read anything about it. I didn't see any evidence about that.
Q. You would agree with me that it was well-documented in the literature for somebody who was a chemist who actually was doing a rigorous scientific literature search as part of a risk assessment for a drug manufacturing process, if they looked, they would have been able to find the literature saying that under the conditions of that process, the sodium nitrite and the processes that were happening could potentially nitrosate the DEA and create NDMA.
You would agree that that information was out there if they had looked, correct?
MR. BERNARDO: Object to the form of the question. Compound. Argumentative.

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Go ahead.
THE WITNESS: I disagree.
BY MR. SLATER:
Q. Fine. You disagree.
Do you disagree because it's your opinion that unless there's an article that replicates the exact conditions of the process that they intended to use, they don't have to think about it as a potential issue?
A. No, I never said that.
I use the general practice of -- of science, right? So every science has a scope, right? You cannot just artificially expand your scope of your understanding by saying this or that is for sure, everybody knows.
I -- my approach is rely on the reference and what's available. So I did my search. I found for -- for the secondary amine reaction, if you know there's a secondary amine, it's documented. But it's not as common as the expert of the plaintiffs claim.
And for the tertiary amine, it's -- it's much more complicated. I didn't know my personally. I never teach. I never really do any

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research before I'm involved in this case.
By reading more recent papers discuss about this, I have no clue about this reaction. So that's how I form my opinion.
I mean, these batches as you showing here, they shows, yes, these batch when they look back, they did find DEAs in their multiple batches.
I just don't see why this will help them to actually figure out because this everything they did here -- they did here is backward. We now sitting 2023 talking about this happening 2003. 2013. I'm sorry.
Q. DEA is a secondary amine, right?
A. DEA is dimethylamine. It is a secondary amine.
Q. And it was well-documented in the literature that a secondary amine could be nitrosated, correct?
MR. BERNARDO: Object to the form of the question. Vague.
BY MR. SLATER:
Q. During the entire time they developed and used these processes, it was

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well-documented in the literature that a secondary amine could be nitrosated, correct?
A. As I said --
Q. You said that, right?
A. I said that secondary amine can be nitrosated. It's documented, right, multiple times. But I said --
Q. That's all I asked you, Doctor. I didn't ask for another speech. I asked if it was well-documented. You agreed. We're fine.
A. No, I said it's documented. I never said it's well-documented.
Q. Okay. It's documented.
A. Thank you.
Q. If ZHP had actually done a literature search, found the literature documenting that a secondary amine could be nitrosated, and they had then said, well, since this could potentially happen in general, let's test for NDMA and they used mass spectrometry, they would have been able to find the NDMA.
Is that correct? Yes, no, or you have no opinion?
A. That --

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MR. BERNARDO: Wait, Dr. Xue.
Object to the form of the question. Asked and answered. Assumes facts. Vague. Compound.
Go on.
THE WITNESS: That's not correct.
BY MR. SLATER:
Q. Okay. What this --
A. You have a lot of hypothetic situation added in there. I cannot really answer question with so many hypothesis. I already state my opinion clearly about these two situations.
MR. SLATER: Okay. Let's -- let's look at this, too. Just -- let's go to the next document.
(Document marked for identification as Xue Exhibit 13.)
THE WITNESS: Now is this 14, 12 or 13?
MR. SLATER: What number is this? 13.
THE WITNESS: Hold on. I'm still loading. I only see 12.

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BY MR. SLATER:
Q. It's only one page. It's the page on the screen. That's the whole exhibit.
A. Yeah, I can see the page on the screen.
Q. All right. Just what we did is, we found on the Internet this Certificate of Analysis from the same company that was discussed in that Table 4.31 we just went through, and you can see it's dated November 25, 2012 just above the table.
And you can see that it shows the triethylamine analysis showed that there was diethylamine in that product.
Do you see that?
A. So I never see this document before.
Q. Do you see that it shows that there was diethylamine noted in the Certificate of Analysis for the triethylamine sold by this manufacturer?
I'm literally just asking you do you see that it documented the presence of diethylamine.
A. I saw this. So there's entry. Because I have to -- because I never seen it

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before, I need to understand what this document is, right? I think that that's reasonable, right?
So -- so there is an entry talk about diethylamine.
So what "WT" stand for?
Q. I'm guessing percentage by weight, but you're the scientist. I'm the guy who failed those science classes.
A. Well, yeah. So I think that that's a number that I need to know what -- what that means.
Q. Okay.
A. I think that's a good guess, but I really don't know what that is.
Q. Okay. Does that prevent you from saying that you can see that --
A. No. No.
Q. -- triethylamine they found that there was diethylamine in the triethylamine?
It's there, right? You see it on the page, right?
A. Well, because --
Q. Doctor, do you see it on the page?
I'm not asking for an explanation

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for all the reasons that you want to tell me it doesn't matter. It's a simple question. So I'll try it cleanly.
On this Certificate of Analysis dated November 25, 2012, for the chemical company that was discussed in the deviation investigation report in Table 4.31, you can see that it documents the presence of diethylamine.
You see that, right?
MR. BERNARDO: Objection. Form.
THE WITNESS: I see diethylamine there. I'm sorry.
BY MR. SLATER:
Q. Okay. Did you ever ask anybody to give you any Certificate of Analysis from any of the suppliers or manufacturers for the DMF or triethylamine that was used in the manufacturing processes for valsartan?
Did you ask for those documents? That's all I'm asking you.
A. Can you repeat again? Because your sentence very long. I got lost in the middle.
Q. Did you ask the lawyers who hired

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you to give you any Certificate of Analysis that they had for the DMF or the triethylamine that was used by ZHP?
A. Well, early on I said --
Q. Doctor, it's a simple question.
Did you ask for a Certificate of Analysis from the lawyers or not?
A. I didn't -- I didn't ask for those.
Q. All right. Did you see any?
A. Sorry. You're -- you're freezing for a second.
Q. Did you see any?
A. What? What? Any of what?
Q. Did you see any Certificate of Analysis for the DMF or triethylamine used by ZHP? Yes or no.
A. I don't remember seeing any.
Q. Okay. Take that down.
Now what we're going to do is, we're going to go to some pages within the DMF, the drug master file that was filed with the FDA, and it's the section on impurities. The module on impurities.
And we're going to go to page --

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A. Hold on. We talk about a new exhibit -- exhibit like 14?
Q. We're going to go to page 100 and --
A. I'm not seeing that yet in my folder.
Q. It's just not there yet, Doctor.
A. Okay. I'm sorry.
Q. Chris is doing it right now.
A. Thank you for reminding me.
Q. No problem.
Let's go to page 147 of 172 first.
A. Please give me a second because I'm still refreshing.
Q. It's okay. I'm just letting him know where he's going. No problem.
(Document marked for identification as Xue Exhibit 14.)
BY MR. SLATER:
Q. I'm looking at page 147 of 172. It says "Discussion about Genotoxicity."
Do you see that?
A. Hold on. Give me a second. I'm still loading and trying to open this.
You said 147?

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Q. It's on the screen, Doctor.
A. Yeah, yeah. Because can you --
MR. SLATER: Help me out, Rich, please.
MR. BERNARDO: He's entitled to take a look at the document, not the page that you have on the screen, Adam.
MR. SLATER: Okay. Well, that's okay. We're going to have to start talking about time issues if we get into them because this has been very, very difficult.
THE WITNESS: Yes, I can see this page now.
BY MR. SLATER:
Q. Great.
This is the section with a "Discussion about Genotoxicity."
Let's now go to the next page, 148 of 172. It says "Discussion on Impurities" at the top of the page. And then it has -- it says "Organic impurities."
"All the potential organic impurities are demonstrated in Valsartan listed as

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follows."
Do you see that?
A. Yes. At the table, right?
Q. Okay. And then let's go to the bottom of the table to the language there. And in the last paragraph, it says:
"Regarding the impurity D through J and hydrolysis product, there is not any high potency genotoxic group, such as, aflatoxin-like-, N-nitroso-, and azoxy-compound has been included in these impurities. And these impurities are demonstrated absence in the drug substance and controlled within the any unknown impurity of NMT 0.10% in the final product. These impurities are no genotoxic risk in Valsartan."
Do you see what I just read?
A. Sorry. There's airplane noise. Can you guys hear the noise?
Q. Do you see the last paragraph on the page I just read?
A. I do see the last paragraph, but I didn't quite follow your -- your -- your reading because the noise outside. I can read that paragraph myself, though.

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Q. It says in part that there's no high potency genotoxic group, such as aflatoxin-like-, N-nitroso-, and azoxy-compound in impurities for the zinc chloride valsartan.
Do you see that?
MR. BERNARDO: Object to the form of the question and the characterization of what the document says.
BY MR. SLATER:
Q. You see what I just read, right?
A. I saw what you just read.
Q. Okay. That was an untrue statement because there was actually NDMA in the valsartan manufactured with the zinc chloride process, right?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: I need to read the -- this table a little bit because I don't remember seeing this.
BY MR. SLATER:
Q. Doctor, it's a very simple question.
When they -- when ZHP represented

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that there were no N-nitroso-compounds, it was -- that was not accurate because there was NDMA in the valsartan produced with the zinc chloride process, correct?
MR. BERNARDO: Object to the form of the question and how you just mischaracterized the document. And he asked to read it to see what the other reference was referring to. So give him a minute to see that.
BY MR. SLATER:
Q. Take a look.
A. (Reviews document.)
So this document is very big. I recall when I first load the document, there's some structures. I want to see the structure of the drugs. Are they anywhere in the document?
Q. Doctor, I asked you a specific question.
Are you now looking to find out if they disclosed the presence of NDMA? I mean --
A. No, no, no.
Q. -- a different copy?
A. I'm asking because they talk about

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this structure G, H, and all the --
Q. It's right above. It's on the same page directly above the language. It's that table right above it.
MR. SLATER: Scroll down a little so he can see it.
THE WITNESS: Yeah, I -- I --
MR. SLATER: Chris, please.
THE WITNESS: What the page number again for this? I went back to the first page. I need to go back.
BY MR. SLATER:
Q. Right there in front of you on the screen. 148. That's literally the table that's being referred to.
A. 148. I'm -- okay. So I'm on 148.
So the reading of this second paragraph that you just read to me regarding to the impurity D through J, N is hydrolysis products, okay? Those -- those compounds.
All right. So what they describe is these compound structure doesn't actually has any of those listed functionalities including nitroso was in the structure, right?

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So, and, therefore, they are not -- they are not qualified as high, you know, toxic compound because they don't have any of those three structures -- groups. And because of that, they are saying they are not quantified -- qualified as high potency genotoxic groups.
And then they say these impurities are -- are -- their -- their presence is actually within the controlled NMT -- I don't know what NMT stands for -- but within the controlled relation. Therefore, they say there's no genotoxic risk.
I don't -- I don't see if there's any problem because they -- these structures, as I saw on the first page of the document, they have none of this containing these listed functionalities. Therefore, they are not high risk and presumably the non-high risk compound has a limit of .10 percent.
Now, they are all okay. That's what they talk about here.
Q. All right. Did they -- did ZHP do any testing for NDMA or NDEA, or any other nitrosamine that you've seen, for the valsartan manufacture with the zinc chloride process at any

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time before 2018 testing?
A. Before 2018, I didn't see any evidence. Because they -- as my opinion, they don't have any clue and they don't have any reason to test. But after, yes, we believe especially at the end of the day, they have the root cause analysis to see what is the possible reason. They raise hypothesis.
Q. Okay. We're going to take that down.
You talked in your report about the July 27, 2007 e-mail sent by Jinsheng Lin to Min Li and others.
Do you recall writing about that in your report?
A. I -- I do.
Q. All right. Did you read Min Li's testimony in his deposition where he talked about what the e-mail said?
A. Well, I -- I read depositions from multiple people. I definitely read Min Li's deposition, but I don't know whether I read every single line of that.
By the way, are you -- are you going

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to sent out another file which I don't see?
Q. I don't know. I haven't decided yet.
A. Oh, okay.
Q. Not sure.
Did you read Min Li's testimony where he testified to what the e-mail said?
MR. BERNARDO: Object to the form of the question. Asked and answered.
THE WITNESS: As I said, if you, you know, if you have a document, I'd like to see it because then we both are clear what we talk about here.
BY MR. SLATER:
Q. I'm talking about the deposition of Min Li.
A. Right.
Q. Did you read the part where he told us under oath, speaking for ZHP as a corporate representative, what the e-mail said?
MR. BERNARDO: Object to the form of the question. If there's a portion of the testimony you're asking if

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he's read, it would be helpful to show him.

THE WITNESS: I -- I read from Min Li's testimony, but I really don't know what line or what section you refer to. It's hard for me to -- to actually speculate.

BY MR. SLATER:

Q. I'm looking at your report. Why don't we look at your report. You have your hard copy of your report right there. Let's go to page 54.

You see your report page 54? You have that in front of you?

A. Yes.

Q. Okay. And right in the middle of the page Section VII, you say in the first sentence that:

"Plaintiffs' experts assert that, in an e-mail dated July 27, 2017, ZHP employee Jinsheng Lin 'acknowledged the impurity he was investigating [in crude irbesartan] was very likely an 'N-NO compound' which 'is similar to the N-nitrosodimethylamine that occurs in valsartan

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when quenched with sodium nitrite.'"

Do you see that?

A. I saw that quote.

Q. And did you read the actual e-mail?

A. I -- I -- I read the e-mail. I would -- I think the e-mail if you -- the e-mail was in both Chinese and then English like a version.

Yeah, I remember reading the e-mail.

Q. Okay. And you say in your report on page 55:

"Mr. Lin's e-mail is written in Chinese, my native language."

So then you say:

"Based on my understanding of Chinese and my expertise as a chemist" and then you go on.

So the question I want to ask you is: In terms of your interpretation of the e-mail, you're relying on your reading of the document in Chinese and your expertise as a chemist in order to interpret it, correct?

A. Well, not just that. I also considered the translate -- translates I got from

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the counsel.

Q. Did you also consider Min Li's testimony as to what the e-mail actually said when he was deposed under oath as a corporate representative speaking for ZHP?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: So, yeah. So it's better that you highlight what he said. I remember reading his testimonies, but I don't know what section you refer to.

BY MR. SLATER:

Q. Well, you didn't actually -- rephrase. Hang on.

You actually didn't talk in your -- rephrase.

You didn't actually quote what Dr. Li said in his testimony, right? That's not quoted in your report, right?

A. I didn't.

Q. When you interpreted what the e-mail said, did you rely on your own reading of the e-mail, or did you rely on Dr. Li's reading of the

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e-mail which he testified to under oath on behalf of ZHP?

MR. BERNARDO: Object to the form of the question. Vague.

THE WITNESS: I mean, for this e-mail, I read in different format, right? They all be kind of different. And then I -- what I read, truthfully, what I did is, I went in to see what the whole article -- what the whole document was really talk about in science.

Because I, you know, I'm an organic chemist. I want to learn because there are confusions. I have to admit there are confusions for me. I don't really understand some part of this in detail.

So I just went in as a scientist to see what the science told me. And then I also, you know, I remember that e-mail also had -- had a -- had an attachment in there.

I -- I specifically asked the counsel to provide that attachment to me.

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I also read that attachment. I believe -- I might be wrong in this. But I believe the attachment only -- I don't remember reading in Chinese. Probably I only read English. I might be wrong on that.

But, anyway, so my -- my -- my -- my opinion was formed solely just based on my understanding of the chemistry of the two full document together to reach to the conclusion.

I don't remember quoting anybody because I, you know, I don't want to kind on anybody side. I just want to see what the science taught me about.

BY MR. SLATER:

Q. Were you aware when you formed your opinion about what the e-mail said and meant that Dr. Li's testimony as a corporate representative of ZHP was binding on ZHP?

MR. BERNARDO: Object to form.

BY MR. SLATER:

Q. Were you aware of that?

MR. BERNARDO: Object to the

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form of the question. Legal conclusion. And still vague as to the reference to the testimony.

THE WITNESS: Well, I can only say when I -- when I --

BY MR. SLATER:

Q. I just want to know if you knew that Dr. Li's testimony was binding on ZHP. All of his testimony -- because he testified as a corporate representative -- that it was binding, and he was speaking for the company.

Did you know that?

MR. BERNARDO: Object to the form of the question. It's a legal conclusion. Dr. Xue is, as we know, not a lawyer and --

MR. SLATER: I'm asking if anyone told him that. I didn't ask if he agrees. So I'm not sure what the objection is.

BY MR. SLATER:

Q. Can you answer, Doctor? Did anyone ever tell you that?

MR. BERNARDO: You concluded

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that it is binding, which is legal.

MR. SLATER: Do you want to take the position that your corporate representative's testimony is not binding on your client? I guess you can kind of float that one when we get to court.

MR. BERNARDO: I want to take the position that it's inappropriate to ask a legal conclusion about binding form of testimony.

MR. SLATER: Okay. You made your objection. You got your objection.

BY MR. SLATER:

Q. Doctor, were you aware -- rephrase.

Did anybody ever inform you that Min Li testified for ZHP as a representative and his testimony was binding on ZHP when you were making choices as to which version of what the e-mail said you should rely on?

I just want to know if you knew that.

MR. BERNARDO: Object to the form of the question. Vague. Calls for legal conclusion.

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BY MR. SLATER:

Q. It's a yes or no. Did anyone tell you that?

A. I -- I don't remember anybody told me that.

Q. Okay.

A. But I...

Q. Did anybody ever give you the typed transcription in English that ZHP presented to the court as their official transcription of the e-mail?

MR. BERNARDO: Object to the form.

BY MR. SLATER:

Q. Translation I should say.

MR. BERNARDO: Object.

BY MR. SLATER:

Q. Let me ask it again.

Did anybody ever give you the translation that ZHP produced to the court as a true and accurate copy of an English language translation of the July 27, 2017 e-mail, which ZHP presented to the court? Did you ever get that translation?

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MR. BERNARDO: Object to the form of the question and the characterization of it. Document. Assumes facts.

THE WITNESS: Well, as I said just now, right? This I -- I read. Honestly, I never ask what translate those are, but I was -- I read two translate along with original Chinese.

I told you just now. I was confused for many points. The translate help a little bit but not really much.

So I solely -- as I said, I solely just rely on my expertise of the organic chemistry, which I'm here for, right?

So I understand what the author of the e-mail was trying to do through -- throughout his own, the full -- the full document and along with the attachment was what was put in there.

So to answer your question, I don't know exactly which one you talk about. Which one. Trying to say what, I

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don't know that.

Are you -- are you adding a new file to my folder?

(Audio malfunction).

(Document marked for identification as Xue Exhibit 15.)

MR. SLATER: All right. I think I just said a whole bunch of stuff and no one heard it.

MR. BERNARDO: That is correct. If you said anything, nobody heard it.

MR. SLATER: Which is probably ideal.

Chris, can you go back to the certification? To the paragraph K, or paragraph whatever that was, 13.

BY MR. SLATER:

Q. All right. Looking at paragraph 13 of Seth Goldberg's declaration, which is dated May 14, 2021, you see paragraph 13 which says:

"A true and correct copy of an English language translation of an e-mail dated July 27, 2017, authored by ZHP employee Jinsheng

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Lin" then there's a Bates number "is attached to this Declaration as Exhibit K."

MR. BERNARDO: Object to the form of the question. Object to asking this witness about a legal document.

MR. SLATER: I'm literally just showing him where it came from, Rich.

MR. BERNARDO: May I finish my objection and you can ask whatever you want.

Object on the grounds of foundation.

Go ahead, Doctor.

MR. SLATER: You're objecting on the grounds of foundation? What's that? Tell me that one so I understand how to ask a better foundation question when I literally just showed him the declaration and the paragraph identifying the exhibit. Tell me what the issue with foundation is so I can fix my question.

MR. BERNARDO: Whether this witness has even seen this document.

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MR. SLATER: That's not a legitimate --

MR. BERNARDO: Or whether he knows what it is.

MR. SLATER: That's not a legitimate objection.

MR. BERNARDO: I disagree.

Go ahead.

MR. SLATER: Okay. Whether he's seen it is a foundation objection? Haven't even asked him that.

All right. I'm going to move along. I'm confident in this question.

BY MR. SLATER:

Q. So now I'm going to show you Exhibit K, okay, Dr. Xue? Exhibit K -- let's go to the document -- is right there on the screen. And at the top it says:

"Bulletin on the preliminary findings about produced unknown impurities in quenching sodium azide for the crude irbesartan."

Do you see that?

A. Can you make this -- make this bigger?

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Yeah, I -- as I said, I read.
Q. It's right there on the screen.
A. Yeah.
Q. Do you see? Do you see the e-mail?
A. I read -- this is translate, not original e-mail, right? So I saw --
Q. Have you seen this translation?
That's -- let me start with a new question.
Have you seen this translation?
A. It's really hard for me to answer this question because I, you know, I read so many things, and this for this particular document, I know for sure I read more than one English translate. I have to kind of read through to see whether I saw this.
Q. Doctor, fine. You're not sure if this is the translation you saw.
Let's go to page 2, and at the top of page 2, it says:
"Through the secondary mass spectrometry analysis, it can be inferred that the additional NO substituent is in the cyclic compound fragment part, and it is probably that it

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is the N-NO compound."
I want to stop there.
You see what I just read, that first part of the sentence at the top of the page?
A. I -- I saw what you read.
Q. Okay. So you can see they refer to the fact that they used mass spectrometry, right?
MR. BERNARDO: Object to the form of the question. Vague.
BY MR. SLATER:
Q. I'll ask the question again.
You see that Dr. Lin who wrote the e-mail refers to a mass spectrometry analysis? You see that, right?
A. I saw, yes.
Q. Now, going back to where I left off. After it talks about what they were seeing in the irbesartan that they were working on, it says:
"Similar to the N-nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite, its structure is very toxic, and its possible production pathways are as follows."
Okay. I want to stop there.

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Do you see what I just read?
Do you see what I just read?
A. (Reviews document.)
Q. Doctor, are you there?
A. That's the first paragraph still, right?
Q. Yeah, it's the first paragraph.
A. Yes, it is what you just read, but this is one --
Q. Doctor, that's what I asked you.
Do you see what I just read?
A. Yes.
Q. So in this translation provided by ZHP, in part Dr. Lin pointed out that there is an N-nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite.
That's what it says on the paper, correct?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. That's what the words on the page say, correct?
A. I -- I --

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Q. Is that what the words on the page say?
A. Honestly, I don't think.
Q. You don't think.
Is that what words on the page say, Doctor?
A. But this is not my approach. I'm here to offer --
Q. Doctor, I'm not asking your approach. I'm taking -- I'm taking this deposition. You filibustered me for like half the deposition.
MR. BERNARDO: Okay. Let's --
BY MR. SLATER:
Q. I'm not really that bitter about it because it's Friday so we're all happy people, but I asked you a very simple question.
Do you see the words on the page showed what I just showed you?
MR. BERNARDO: Object to the form of the question. Object to the argumentative nature of the question.
Dr. Xue, he's just asking you to agree or disagree that he read that

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properly from what's on the page.
THE WITNESS: Sorry, Rich. Can you repeat what you said? Because you were just -- I didn't hear any basically.
MR. BERNARDO: Dr. Xue, he's just asking you if you agree that he read what's on the page correctly.
THE WITNESS: Oh, by reading, yes, I don't have any problem with the reading part.
BY MR. SLATER:
Q. So in this e-mail, according to the translation from ZHP, Dr. Lin pointed out that there's NDMA in valsartan and it's produced by the quenching of valsartan with sodium nitrite.
That's what that phrase says, correct?
MR. BERNARDO: Object to the form of the question. Assumes facts.
Go ahead, Dr. Xue.
BY MR. SLATER:
Q. That's what it says, right?
A. That's -- that's one form of the

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translation, right? So if you look at other translation, they are different forms. And plus, even if just this -- this form of translation, right, that -- that N-nitrosodimethylamine group is not talk about NDMA. It talk about a group that is similar to NDMA.
So what I really trying to say is, you know, if you put up one thing and to say whether this is read correct or this or that, I don't think that's a complete understanding of what the e-mail is.
And point out. When I read this, I first read in Chinese. I found there are puzzles I cannot read and understand, and then I went through the science.
I went through all the translate that provide to me, too. That explains some, but really not help me to -- to grab the whole information.
I mean, I'm here as an organic chemist, right, trying to offer my opinion with a neutral way, but I don't think it's right that when you have multiple of these translate, you point one to say, is this word correct or not?

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I mean, I -- I speak Chinese, right? So it's Chinese sometimes -- how to say this? It's not -- it's not like you can word to word translate things and say, oh, this must be accurate, right?
I didn't ask, but I assume everything provided to me, they are not just random translate. They are -- they are -- they must be some, you know, certified translate and then provide that to me, right?
So everybody's translate has some value there. I can't answer this particular one at all. I'm not saying that or any other ones I saw.
So what I really, my portion, I mention that, right? I went to the science. They talk about irbesartan, right? That clearly show in their theme, they talk about reaction happened on irbesartan. And then, too, as example to show this might be a common, common, possible common reaction.
He also in his attachment showed this particular reaction also happen on the drug molecule. In this case, it's a deoscillated

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irbesartan -- sorry -- valsartan.
The common theme as I show in -- see there in my report carefully I say, okay, so this is what he actually really mean to show. There's a reaction definite on this reactive nitrogen on this particular drug, irbesartan, and also this can be a general or a common theme when you have a similar reactive, a group of nitrogen atom on deoscillated valsartan and that can be actually parallel.
He -- I honestly I have no clue how he actually hypothesized these things are highly toxic. That's where -- where my puzzle come from. I don't know. I mean, I respect everybody, but this person, this Dr. Jinsheng Li, I don't see he show any evidence to me showing either one of these compound are highly toxic.
Because, you know, you cannot assume nitroso-compound are highly toxic. He put in there. That confuse me a lot.
But I can only say my point or my conclusion or my opinion is, he's talked about irrelevant reaction, and that reaction can be a common theme as he warn his boss or, you know.

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Yeah. So in the e-mail say, okay, look, there might be something we pay attention. That's all I learn from -- from -- from the whole thing.

I really don't want to get involved in this, like, look at this particular one translate, tell me if this is correct.

Yes, I'm Chinese.

Q. Doctor, are you just going to talk until my time is up? I mean, is that what you're trying to do?

A. I'm trying to help. I really offered --

Q. You're not helping. You're not helping. You're not -- you're not anywhere close to helping. With all due respect, I don't know what you're doing.

You're talking about -- you're like off in all different places. I don't even know what you're talking about. I'm just being really honest. I don't know what you're doing.

A. Well, I --

MR. BERNARDO: Dr. Xue.

BY MR. SLATER:

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Q. I don't even know what you're talking about anymore, Doctor. I'm totally baffled. You've baffled me.

MR. BERNARDO: It's late on a Friday afternoon. Let's just, Dr. Xue --

MR. SLATER: I'm laughing. I mean, I'm actually smiling. I'm not yelling at him.

MR. BERNARDO: I know. Adam, I'm not accusing you of yelling.

MR. SLATER: I think I'm being a pretty good sport under the circumstances.

MR. BERNARDO: Dr. Xue, just please listen to Mr. Slater's questions and try and answer them as best you can. I know it's late. I know you're not feeling well.

Adam.

BY MR. SLATER:

Q. Okay. Dr. Xue, it was a true statement when Dr. Lin said it that N-nitrosodimethylamine was produced by the quenching of valsartan with sodium nitrite.

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That's a true statement with regard to the zinc chloride process, right?

MR. BERNARDO: Object to the form of the question. Assumes facts.

BY MR. SLATER:

Q. It's a true statement, right?

You already told me that's -- that's -- that's how it was caused. That's the point when the NDMA was created during the quenching, right?

A. No, I didn't.

Q. Yes or no.

A. I didn't.

Q. Hold on. Stop. Stop. You disagree.

So now your opinion is that the NDMA in the zinc chloride process didn't form during the quenching process.

Is that now -- you're now -- you don't agree with that? Yes or no.

A. Sorry. I'm laughing.

Q. There's no more speeches, Doctor. The speech part of the day is over. So you're going to give direct answers, please.

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A. All right.

Q. It's a very simple question.

Do you agree or disagree that the NDMA formed in the zinc chloride process during the sodium nitrite quenching step?

A. After 2018 when the whole thing start to show, everybody including myself learned NDMA can form during this process.

Q. Thank you.

A. I never talk about this.

Q. So --

A. But now we look at the e-mail was prior to that.

Q. Doctor, you got to --

MR. SLATER: Rich, I'm not going to let him do this.

MR. BERNARDO: Dr. Xue. Dr. Xue.

MR. SLATER: I'm not going to let him do this anymore.

MR. BERNARDO: Okay. Adam, can we just take a brief break and I'll see if I can --

MR. SLATER: I mean, I'd

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rather not do it in the middle of going through this e-mail segment.
MR. BERNARDO: Yeah, I know. Further --
MR. SLATER: I really wanted to. You could tell him on the record to stop giving speeches and just answer my questions.
MR. BERNARDO: I'm not going to say.
Dr. Xue, I know it's late. Just please listen to Mr. Slater's questions. If there's more to add, I'm permitted to ask you after Mr. Slater is done and you can add it then.
So, please, just answer Mr. Slater's questions. I know this is confusing with the translations and it's late.
BY MR. SLATER:
Q. All right. Let's be very clear.
In the zinc chloride process --
A. Right.
Q. -- do you agree that the NDMA formed

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when the quenching occurred with the sodium nitrite? Is that when the NDMA formed?
A. Now, yes, everybody learn.
Q. Okay. In July of 2017, that's what Dr. Lin said in this e-mail -- it's right there in front of you -- that the NDMA produced by the quenching of valsartan with sodium nitrite. He said that in 2017.
You see that right in front of you, correct?
MR. BERNARDO: Object to the form of the question. Assumes facts. Asked and answered. Mischaracterizes his prior testimony about that sentence.
THE WITNESS: I disagree. Because as I said, you know, this is one form of the translate. And even the original Chinese when I read, I was confused.
I -- I read more than this. I don't know. This might be one of the two that I read. This might be the third one that I read. I -- I cannot remember exactly, but I cannot just look at one

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translate, word by word translate to say this is about NDMA, right?
So I remember clearly there's one translate. They have a different translate there as well.
BY MR. SLATER:
Q. How many translations did you see?
A. Well, I honestly don't remember. I think two.
Q. Was this one?
A. I don't know it's one of the two. I -- I don't remember.
Q. Okay. Now, let's scroll down to the bottom half. Underneath the little diagrams, the second paragraph. It says in the second sentence of the second paragraph down there:
"This is a common problem in the production and synthesis of sartan API."
Do you see that?
MR. BERNARDO: Object to the form of the question. Same objection with respect to the use of this document.
BY MR. SLATER:
Q. Do you see the sentence I just read?

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A. By reading, yes.
Q. So according to this e-mail as translated by ZHP, Dr. Lin advised in the e-mail that this problem with the creation of N-nitrosodimethylamine group due to quenching of Valsartan with sodium nitrite is a common problem in the production and synthesis of sartan API, correct?
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. That's what the e-mail says, right?
MR. BERNARDO: Object to the form of the question. The characterization of the document. It assumes facts.
Go ahead, Dr. Xue.
THE WITNESS: I disagree as I --
BY MR. SLATER:
Q. Fine. You disagree.
Based on your interpretation, right?
A. Based on my understanding of the whole article -- the whole e-mail with the

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attachment.
Q. Which includes your own interpretation and translation of the e-mail based on your reading of the Chinese language, right?
A. Based on my reading of everything, not just the Chinese. Also every translate that provide to me. Also the reference that attached to this e-mail as well. That's -- that's how I define myself.
Q. Okay. He then says:
"It is recommended to improve to other quenching method, such as NaCIO, in addition to optimize the quenching process for sodium azide in valsartan."
So he's literally pointing out we need to optimize the quenching because he's pointed out that the quenching of the sartans is causing nitrosamines to form.
That was a good suggestion, right? Let's optimize the quenching so we don't create nitrosamines. That was a smart suggestion, correct?
MR. BERNARDO: Object to the form of the question, to the use of this

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document, to the translation, and to the characterization of his prior testimony.
Go on.
THE WITNESS: Well, something Dr. Jinsheng Lin is talking here. I never against that. I think that's my understanding as well.
However, the reaction he refer to here, also clearly to me after I read the whole thing and I see the whole situation is the reaction to form what he join up there, the nitroso-compound.
Also, the deoscillated valsartan in that patent also can form a nitroso-compound. These two compounds he hypothesized can be, and he then offered a potential optimization. Say, hey, if we not using the quenching, using other quenching as people already reported in their patent, we might be able to get around these potential -- potential nitroso-compound that he raised.
I think that I agree with you. To look for a different quenching process

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is what he offered to do. I think to me it's definitely some option you can actually consider to do that that's -- that's one of them.
But the two reaction they talk about is actually these two I mention. Sorry I confuse you first place, but it's --
BY MR. SLATER:
Q. It's not confusing me, Doctor. You're just eating all my time up.
A. But these are the two reactions he talk about, and so he -- he suspect these two compound, nitroso-compounds, they can be highly toxic, which I don't agree. I don't know where he gets supported from.
But I think as an employee seeing nitroso-compound like these two and warn his boss about this as a potential and then suggest some potential solution for this, I feel this -- this -- this is logic.
Q. If we go down to the last paragraph, he talks about the patent?
A. Right.

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Q. He talks about the fact that they proposed that the use of NaNO2 -- that's sodium nitrite, right?
A. Correct.
Q. That sodium nitrite quenching will produce N-NO impurities. And then he says:
"In the meanwhile, our Huahai crude valsartan was detected by LC-MS."
Do you see that?
A. Correct.
Q. So he's pointing out that the nitroso-compound that they detected in their valsartan, they detected it with LC-MS.
That's what he's saying, correct?
A. What they were saying is the deoscillated valsartan. As I show you in my report, right? That compound can be nitrosamine. So that's the compound they talk.
I just want to make -- make it clear what we talk about here. They not talk about valsartan the drug itself get nitrosylate. To my knowledge today they ask me there still be no chance that you can do nitrosylation on valsartan drug itself. That's my -- my -- my honest

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feeling.
What the patent does and what the patent show us is this compound deoscillated valsartan can actually get nitrosylation reaction to give you this. I believe they call it impurity K maybe, right? So they -- they talk about that, right?
So it's not talk about valsartan at all or anything about even. This -- this whole art -- this whole document has nothing to do with NDMA or NDEA.
Q. Well, where he says -- let's go back up to the top of the document. Then we'll move to something else.
Where he says that what he was seeing in the irbesartan was similar to the NDMA produced by the quenching of valsartan with sodium nitrite, that's relevant to this case, right?
MR. BERNARDO: Object to the form of the question and the characteration -- characterization of the documents being used.
Go on.
BY MR. SLATER:

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Q. That's present -- that's relevant to the case, right?
What was happening with valsartan and how the NDMA was formed, that's relevant, right?
MR. BERNARDO: Same objections.
THE WITNESS: Even if -- even if we only look at this translate, right, not consider any other things. First of all, I think that's biased already.
Even if this, they clearly talk about the compound happen during the valsartan process where the deoscillated valsartan can actually react to form a nitroso-compound. These are --
BY MR. SLATER:
Q. I'm sorry, Doctor.
Where does he say -- where does he say valsartan -- deoscillated valsartan?
It says "quenching of valsartan with sodium nitrite."
That's what it says in those words, right?

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A. No. No. I have to -- I have to be clear.
Q. No. No, Doctor, we're not. You don't get -- you don't get to run the deposition. That's what it says. It says quenching of valsartan.
MR. BERNARDO: He's trying to explain why he disagrees.
MR. SLATER: This is -- he disagrees that the word says "valsartan"?
MR. BERNARDO: Let him finish his answer and he'll explain what he means.
MR. SLATER: You know what? I withdraw the question. So we're not going to hear the speech.
BY MR. SLATER:
Q. If I'm correct that Jinsheng Lin said in this e-mail that there was NDMA in valsartan and it was formed by sodium nitrite quenching, and that was known in July of 2017, does that impact any of your opinions?
If that's the case, does that impact any of your opinions in this case?

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MR. BERNARDO: Object to form.
BY MR. SLATER:
Q. Yes or no. It's a simple yes-or-no question.
MR. BERNARDO: Object to the form of the question. It calls for speculation. Assumes facts.
Go on.
THE WITNESS: Well, you said a lot of assumptions, right? Let me -- let me walk through this.
You said if I -- if I -- if I just --
BY MR. SLATER:
Q. You don't understand the question. I'll ask it again. I didn't have a lot of assumptions. Let me ask it again.
Well, let me ask you this.
In July of 2017, there was NDMA in the valsartan manufactured with the zinc chloride process, and as we talked about before, the NDMA formed during the sodium nitrite quenching, right?
A. So after all these analysis, yes, we now know that at that time or even earlier it was

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formed. But nobody knows till 2018, right.
Q. Well, if I'm correct -- well, rephrase.
If Min Li is correct in how he translated the document when he read it under oath for ZHP that the e-mail said that what they were seeing in the irbesartan was similar to the NDMA in valsartan which was created by the sodium nitrite quenching, if that is what the e-mail said, then people within ZHP knew about the issue with the NDMA in July of 2017, correct?
MR. BERNARDO: Object to the form of the question. Vague. Object to the characterization of Min Li's testimony. Assumes facts.
Go ahead, Dr. Xue.
THE WITNESS: Well, I think I read Min Li's depositions. I read -- I don't remember exactly what he said.
I don't think your characterization saying he agreed with everything that you just said. I don't remember it clearly get that sense. I remember he somehow -- I don't know

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what -- what -- what translate or whether the -- what you are showing or discuss with him about any form.
I don't remember that, but I remember he was pretty like -- I don't know -- surprised or something. I don't know whether he get a chance to read this before.
I just have many questions. Like whether he actually considered. I mean, you actually showed him the -- the attachment. All these I don't know. I don't want to speculate.
As I said, I'm here. I'm an expert.
BY MR. SLATER:
Q. All right.
A. I just want to tell the truth on what I actually went in to see all these documents provide to me. I honestly judge based on my understanding of the science. I try to explain to you. Although you say I confuse you, but I really try my best, right? I wrote that in my report as well. Yeah.

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Q. If ZHP knew -- rephrase.
If Jinsheng Lin -- well, rephrase. I'll ask it straight-out.
If the e-mail says that -- I'll ask it even differently.
If ZHP knew that there was NDMA in the valsartan as of July 2017 and never disclosed it, that would be inexcusable, right?
MR. BERNARDO: Object to the form of the question. Argumentative.
Listen to his question, Dr. Xue.
THE WITNESS: So you're asking if -- if -- if ZHP knew NDMA present prior to this e-mail? Was that your question? Then they will be inexcusable? That was -- that was what you asking?
BY MR. SLATER:
Q. If ZHP knew there was NDMA in the valsartan in July of 2017 or earlier and didn't tell anybody, that would be inexcusable, right?
A. If that's the case, yes.
Q. And you're just trying to come to an

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understanding of what they knew based on your reading of multiple translations and your own interpretation of the Chinese version of the e-mail and whatever else you saw.
You don't actually have an opinion as to what the e-mail really said because you're looking at so many different sources of translation, right?
MR. BERNARDO: Object to the form of the question. Object to the characterization of his prior testimony.
THE WITNESS: I disagree. I think I clearly offered my opinion on this one.
BY MR. SLATER:
Q. And part of that opinion is based on your own reading of the document in Chinese, right?
A. That's definitely part of it. There's other parts. All the information. I definitely consider everything that -- that came to me I asked for together to form my opinion.
MR. SLATER: Let's take a break.

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THE VIDEOGRAPHER: Time right now is 5:50 p.m. We're off the record.
(Recess.)
THE VIDEOGRAPHER: Time right now is 5:38 p.m. We're back on the record.
BY MR. SLATER:
Q. On page 55 of your report at the bottom, in talking about that July 2017 e-mail you say:
"In addition, ZHP employees who have testified about the e-mail have made clear that 'due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied' with respect to Irbesartan, and therefore ZHP 'was unaware of the further reaction between degradation products and raw material' related to Irbesartan."
Do you see that?
A. I do.
Q. And you cite in note 122 to Min Li's

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deposition transcript.
You see that?
A. (Reviews document).
Q. Doctor, this is your report. It says 122 at the end of the sentence I read at the bottom of the page?
A. Yeah. Sorry. Sorry. I was --
Q. That's Min Li's deposition, right?
A. Yes.
Q. And after you say that in your report, you say:
"As a result, Mr. Lin's e-mail discussing Irbesartan could not have been addressing the formation of nitrosamines as a result of the potential degradation of DMF, which is what plaintiffs' experts assert resulted in the formation of nitrosamines during the zinc chloride process for Valsartan API."
You see that?
A. I saw that.
Q. So you're relying in part on that testimony from Min Li for your understanding and interpretation of the e-mail, correct? That's what you're saying in the report?

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A. About why they -- they didn't pursue anything on this irbesartan because it's not relevant.
Q. Now what we're going do is, I'm going to go to the testimony you cited, which is Min Li, April 22, 2021, page 528 line 14.
And you can see at line 14 it says:
"We have on the screen Exhibit 212, which is a report, and the topic title is 'Investigation regarding an unknown impurity,' and then in parentheses 'Genotoxic impurity' with regard to valsartan.
"Do you see that?"
A. Do I have that document also in my folder?
Q. I don't know what you're asking me, Doctor, but I'm showing you the transcript right on the screen, please.
A. Well, yeah, but can I see the -- the -- you put everything in my --
MR. SLATER: It's there.
What exhibit is it?
Exhibit 16 is the transcript.
(Document marked for

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identification as Xue Exhibit 16.)
THE WITNESS: Can you please let me know the page number as well?
BY MR. SLATER:
Q. It's page 528 line 14.
A. Well, it is loading on my computer. So give me a second.
Still loading, though.
Q. That's all right. Take all the time you want. At some point, I'm going to run out. It's okay.
A. For some reason, this way it's just loading. The circle is just going.
Q. Do whatever you want. Take as long as you want. I mean, it's only -- I've only lost hours in this -- in this deposition already. It's okay.
A. Well, this is not me, right? So.
Q. I don't really understand why you need to do that. I literally just showed you what you cited in your report, but okay.
MR. BERNARDO: Object to the form of the question. I don't think it's inappropriate for witness to actually ask

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to see a transcript of what you're showing one page. That's the way it would ordinarily be done if we were in person.

MR. SLATER: That's okay. I think I've been extraordinarily easygoing under the circumstances here. I've got a smile on my face. So it's okay.

I assume you're going to be reasonable if all of a sudden we get down to my seven hours so we don't have any issues. But, you know, you can do whatever you want.

THE WITNESS: For some reason, this -- this document is really loading like right now.

MR. SLATER: Shall we keep the clock going while his document is loading? What do you want to do, Rich, just wait until the clock is out?

Why don't you let it spin for 30 more minutes. Take whatever time you want.

MR. BERNARDO: All right.

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Adam, come on. Let's just chill here. If you want to go off the clock, go off the clock. It's your deposition. He's entitled to read the document.

MR. SLATER: All right. So let's go off the clock and he can read the deposition.

Yeah. Let's go off the -- off the clock and you probably should download the transcript I'm told.

THE WITNESS: How can I? Because I was -- I was doing everything else today was -- was fine. So only this one 16 when I click it, it just didn't.

BY MR. SLATER:

Q. If you go to the folder, the document is there and you can download it.

MR. HENRY: There's -- there's a G with three periods next to G. Click that and go to options to download it.

THE WITNESS: When I click the three dots, it only says the direct link of this. Or I can download all files it says.

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Oh, this one. Okay. Let me try this. Okay. I'm downloading now.

Okay. Great. It looks like it's downloading. We can go back to talk.

MR. BERNARDO: Well, let's wait until you have it, Dr. Xue.

THE WITNESS: Oh, okay. I'm opening it.

BY MR. SLATER:

Q. It's okay.

A. Okay. It's up here.

MR. BERNARDO: Why don't you get to the page that he's referring to, Dr. Xue.

BY MR. SLATER:

Q. Yeah, read it. You said you want to read it. It's okay.

I'm not on the clock, Doc. You can read the whole deposition if you want. I don't mind.

A. (Reviews document.)

Yeah, I think I read this page and we can go back to talk because I really want to go

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home tonight.

Q. I don't care when I go home. I'll work as late as we need to. I honestly don't care. If I get done with you, I'm going to work on other stuff all night. It doesn't matter.

A. Please consider I'm still COVID-positive.

Q. So are you ready to answer questions about this?

A. Yes. Are we back on the clock?

Q. Can we go back on?

All right. We're going.

Looking at the testimony you cited in your report, it refers to the fact that this report that you cited is the "Investigation regarding an unknown impurity" and then parentheses "Genotoxic impurity" with regard to valsartan.

You see the testimony says it's a report regarding valsartan, right?

A. Right.

MR. BERNARDO: Object to the form of the question and the characterization of his testimony.

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THE WITNESS: Yeah. By reading that section on line 14 to 18, that was question asked about.
BY MR. SLATER:
Q. You said in your report that that report that I was asking Dr. Li about had to do with irbesartan.
So when you said that in your report, you were incorrect, right?
MR. BERNARDO: Object to the form of the question.
THE WITNESS: Well, with this short time, I really don't recall what I was reading when I write that part. I cannot say yes or no this easy. Because I think my point there was -- was fairly clear.
That whole e-mail case was about irbesartan, and then they talk about why they didn't do further study because it was just a lab scale discovery or development, not even in the real factory yet. So they decide not pursue any further of that.

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That's what I meant to -- to show there.
BY MR. SLATER:
Q. You said in your report when you were talking about why the e-mail means what you think it means and what you told us you think it means, that one of the reasons for that was because of that testimony from Dr. Li with regard to what you thought was a report about irbesartan.
That's what you said on page 55 and 56 of your report, correct?
It's a yes-or-no question. That's what you said, right?
A. I hope it can be a yes-or-no question but really is not.
Q. Is that what you said in your report? Did you refer to this as being -- that you said witnesses test -- rephrase.
You said in your report on bottom of 55:
"In addition, ZHP employees who have testified about the e-mail have made clear that 'due to insufficient extent and depth of process research at the early stage, as well as

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insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied' with respect to Irbesartan, and therefore ZHP 'was unaware of the further reaction between degradation products and raw material' related to Irbesartan."
Then you say:
"As a result, Mr. Lin's e-mail discussing Irbesartan could not have been addressing the formation of nitrosamines," etc.
Okay. So you were -- you were basing your opinion in part on that testimony relating to irbesartan.
That's what your report says, right?
That's what the report says, Doctor, right? It says "irbesartan," correct?
A. Yes, I wrote that.
Q. Okay. And now let's go to the bottom of page 529 line 17, which is part of the testimony you cited for this proposition.
If we look at page 529 line 17, it says -- looking at this report about valsartan under the heading of 5.2 "Control strategy," it

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says:
"'Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied, and was unaware of the further reaction between degradation products and raw material.'"
Now having seen that that relates to valsartan, that's important that ZHP acknowledged in an internal document that they did an "insufficient extent and depth of process research at the early stage" and "insufficient study and understanding of potential genotoxic impurities."
That's important that ZHP stated in a document that that occurred, correct? That's of importance, right?
A. I disagree because --
Q. Fine. You disagree. That's it. That's what I asked you. You disagree.
So let me ask you.
A. Can I explain, though?
Q. No, you can't because I asked you do you -- is that yes or no, you said you disagree.

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Your lawyer can ask you five hours of questions after this if you want.

So let me go to the next step.

So you're saying that ZHP admitted in an internal document "insufficient extent and depth of process research at the early stage" and admitted "insufficient study and understanding of potential genotoxic impurities," that doesn't have any impact on your opinions regarding the adequacy of their risk assessment into the scientific reactions.

That's your testimony, correct?

A. What I'm saying is this irbesartan product is a totally separate project they are working on. Although they both called sartans, they have involve totally different process.

In this particular case, they are in the baby stage. They are still in the lab scale discovery stage. They are not talk about any API process or anything yet. They only talk about in lab space the possibility of producing irbesartan. I said they found this potential problem.

Q. Dr. Xue, the whole point that I'm making to you is that that statement about

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"insufficient extent and depth of process research" and "insufficient study and understanding of potential genotoxic impurities" -- I don't know if you're catching on -- they wrote that about valsartan, not about irbesartan.

Do you not realize that even now after I just showed you?

A. I disagree.

Q. Okay. So you think that that document that you're -- that's being quoted here in Min Li's testimony is about irbesartan?

A. Well, you showed me this -- this single paragraph. You talk about genotoxic impurity regard to valsartan. I -- I don't know the linkage between here and what I wrote here.

Q. There is no linkage. That's the whole point I'm trying to show you, Doctor.

A. Right.

Q. Is when you wrote in your report that that testimony by Min Li had to do with irbesartan, I'm pointing out to you that you were wrong in your report and it actually had nothing to do about irbesartan. It was about valsartan.

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It was reported about valsartan.

Are you just realizing that for the first time right now?

I assume you are or you would have changed your report, right?

MR. BERNARDO: Object. Object to the form of the question. Argumentative. Object to the characterization of the document.

BY MR. SLATER:

Q. I'll restate then.

On that point --

A. I don't think I --

Q. -- Min Li's testimony at the bottom of page 529, he's not talking about irbesartan. He's reading from a report about valsartan.

You didn't realize that, did you?

MR. BERNARDO: Object to the form of the question. The characterization.

BY MR. SLATER:

Q. You're just realizing when I'm telling you, right?

Because your report said it was

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about irbesartan. I'm pointing out to you it's about valsartan.

You didn't know before right now, right?

MR. BERNARDO: Object to the form of the question. Vague and the characterization of the prior testimony.

THE WITNESS: I really don't think it's clear to me what you are talking about. I think I --

BY MR. SLATER:

Q. All right. I'll tell you right now it's not clear.

Look at the bottom of page 529 -- it's right on the screen -- line 17 where it says:

"Under the heading of 5.2, 'Control strategy.'"

What I'm pointing out to you is what it says right after that. They're talking about valsartan. They're talking about their work with valsartan, not irbesartan.

MR. BERNARDO: Object to the form of the question.

BY MR. SLATER:

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Q. I assume this is the first time you're realizing that, right?
MR. BERNARDO: Object to the form of the question. Argumentative.
THE WITNESS: No. I'm here to answer questions that I can understand what the question is. I see --
BY MR. SLATER:
Q. Doctor, I showed you on the prior page that the document was identified was a report about valsartan, not irbesartan.
Your report is wrong. You called it irbesartan. That report is not about irbesartan. This language at the bottom of page 529 was written by ZHP people about their assessment of the process for valsartan.
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. You didn't realize that before right now, correct?
A. Are you trying to -- are you trying to accuse me that I use the wrong word in my report? Because I honestly --

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Q. No, I'm not accusing you of anything.
What I'm pointing out to you is that when you said this language was about their irbesartan investigation, I'm pointing out to you that you are wrong. It was actually about valsartan.
MR. BERNARDO: Object to the form of the question.
BY MR. SLATER:
Q. And what I'm asking you is: Now knowing that they admitted in an internal document "insufficient extent and depth of process research" and "insufficient study and understanding of potential genotoxic impurities," that's important to you now, knowing that ZHP admitted internally they didn't do an adequate research and they didn't have adequate understanding.
That matters to you as an expert, right?
MR. BERNARDO: Object to the form of the question. Characterization.
BY MR. SLATER:

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Q. Does that matter to you?
A. I don't think that's my opinion.
Q. Is that --
A. I don't think that's my opinion at all.
Q. I'm sorry. What?
A. I'm sorry. I'm sorry. I didn't hear you just now.
Q. I said: Does that matter to you in drawing your opinions that now you know that ZHP internally admitted "insufficient extent and depth of process research at the early stage" and admitted "insufficient study and understanding of potential genotoxic impurities"?
That's a significant fact to an objective expert who's actually trying to get to the truth, right?
MR. BERNARDO: Object to the form of the question. Object to the characterization. Object to this line of questioning and the inability of the witness to be able to look at this and consider what you're trying to say in order to answer your question.

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Go on.
BY MR. SLATER:
Q. It's important, right?
A. No, I really -- I don't understand this. I -- I -- my opinion was clearly state through my understanding of this e-mail what this about, why they didn't pursue this case afterward.
Q. Doctor, this testimony has nothing to do with the e-mail. That's the point I'm making to you.
This testimony by Min Li, this has nothing to do with the e-mail.
You drew -- you drew a connection between this testimony and this valsartan report to irbesartan and the e-mail that nobody has ever made. There is no connection. That's the point I'm making to you.
Your report is incorrect and now that you're seeing that, you need to rethink your opinions, right?
A. No, I don't. I really don't.
Q. Okay. So --
A. Because I don't -- I don't know you show me this testimony. So what is the back --

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why you show me this page? What you want -- because there's only one --

Q. Because you cited it in your report. On page 55 and 56 in reference number 122, this is the testimony you cited, Doctor. You cited it thinking that Min Li was talking about irbesartan, but he wasn't. He was talking about valsartan.

He was -- there's a report admitting insufficient research.

A. I might -- well, that might be my typo, might be my mistake of -- of citing. If that's what you accuse me, I, you know, I have nothing against that. Because I may just put a wrong line or I may put that to my human error. I take it, whatever responsibility that is.

But I, you know, apparently I didn't intend to cite anything that is --

Q. Okay.

A. -- wrong.

Q. So now -- so having said that, now that you know that when Min Li was testifying here he was testifying about an internal report about their valsartan research, and he admits that they did insufficient process research and they had

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insufficient study and understanding of potential genotoxic impurities, if -- if that's true that ZHP said that about their valsartan and the work they did on valsartan, do you agree it's something you should take into account in forming your opinions?

A. I totally disagree. Because if that's my human error, just put it on me and say, oh, that's what you mean. I cannot do that, right? So you cannot say because I -- I got the wrong line of citation, you say, oh, this is what you say. I mean, ZHP already know they didn't do enough of good work of risk assessment for their valsartan.

So I'm -- I'm here, you know, as a scientist. I spend the whole day trying to say based on my knowledge why these three are my opinions.

I told you, don't agree that, you know, from any point -- point of Min Li's deposition show that they already know they have insufficient studies. All these three already admitted.

I just -- I don't know where they

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come from. I told you. I don't agree with that.

Q. If I'm correct that ZHP in the internal report wrote the language that you see there starting on line 18 on page 529 of Min Li's April 22, 2021 deposition, that's important for you to consider in forming your opinions.

It's something you need to at least take into account, right?

A. You know, again, your question is so hypothetic, right? You almost ask me if they agree that they did something wrong, are they wrong, right? So that's --

Q. No, I'm asking you if they agree that there was "inadequate extent and depth of process research at the early stage" and "insufficient study and understanding of potential genotoxic impurities," is that something you should take into account in forming your opinions about the adequacy of their risk assessment?

A. Well, it's -- we talk about different things, right? So this project that we talk about when they have these comments about insufficient this or the depth of this, it's baby stage projects, right?

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So when you have these there in the labs and you see some obvious situations. Sometime, you know, I do the same. When my postdoc come to me and say, hey, we try your idea. You know what? After I try a couple reactions, I see something really weird happen. What we going to do? If he has another project which is important, I may just say, okay, let's -- let's shelf that for now and we can worry about that.

I don't think that has any revision with a different product of the same postdoc. He's trying to put something into animal by injection and then he talk about, okay, let's -- let's control that and try to verify this to a high quality so we can do.

I honestly -- I don't know, right? So I'm trying very hard to, right, to tell you the truth of what I feel.

Q. All right.

A. It's hard.

Q. Let's try this one last time.

In forming your opinions, do you agree --

A. Are you talking?

Q. I'm trying to. Do you hear me? I think your thing keeps freezing.
A. Well, you talk -- talk aloud just now. I didn't hear anything you talk about.
Q. You hear me now?
A. Yes.
Q. I'm really trying to ask a very what I think is a straightforward question.
If I'm correct that when Min Li testified about this report, the report was talking about valsartan and that they had an "insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities," you would agree with me that's important to you to at least consider in forming your opinions about whether or not ZHP's risk assessment was adequate.
You'd agree that it's at least something you have to take into account, right?
A. I disagree. As I said, there's two stage of development. If there for those babies, early stage, very early stage, you have very different risk assessment toolbox that require.



I'm not a regulatory scientist. The regulation must be different, right?
So if a postdoc come to me say, this first step you design not working, then I might just say, okay, that's it. Let's try a different project or try a different thing.
I won't -- I won't use, apply a totally same risk assessment requirement to -- to other project like they are late stage. They already be almost ready to get to animal. So I don't agree with that.
MR. SLATER: All right. I'm going to reserve whatever time I have left and, Rich, I guess if you requestion and I need to follow up, you and I can talk about time. I'm not looking to argue with you. I think I've been pretty patient. We can figure it out.
MR. BERNARDO: I think we can figure it out.
MR. SLATER: Go off the video.
THE VIDEOGRAPHER: Time right now is 6:23 p.m. We're off the record.
(Recess.)



THE VIDEOGRAPHER: Time right now is 6:41 p.m. We're back on the record.
EXAMINATION
BY MR. BERNARDO:
Q. Dr. Xue, I'd like to ask you just a couple of questions on behalf of ZHP, and I'd like you to turn to page 55 of your report.
A. Yes, I'm on that page.
Q. And I want to go back to the questions that Mr. Slater just asked you with respect to the testimony that you cite, which you have a Footnote 122.
Do you see where I am?
A. Yes, I do.
Q. Okay. Have you had a chance to take a look at that over the break?
A. I did.
Q. Okay. Dr. Xue, if Mr. Slater is correct that there's an inadvertent error there or that there's an error there that that testimony does not relate to irbesartan but, rather, relates to valsartan, does that affect your opinion with respect to the July 17, 2017 memo -- sorry --



July -- yes -- 17, 2017 e-mail in your report?
A. No, it doesn't.
Q. Does it -- does it change any of your opinions in your report?
A. It don't change any of my opinions.
MR. BERNARDO: Okay. That's all I have.
MR. SLATER: Well, in that case, dinnertime.
MR. BERNARDO: All right. Thank you very much, Dr. Xue. I hope you're feeling better.
Adam, enjoy your dinner.
MR. SLATER: You, too. Go off.
THE VIDEOGRAPHER: Time now is 6:42 p.m. Off the record.

(Deposition concluded at 6:42 p.m.)

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ERRATA SHEET

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DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the _____ day of _____, 2023.

_____
FENGTIAN XUE, PHD



CERTIFICATE OF REPORTER

DISTRICT OF COLUMBIA )

I, DENISE DOBNER VICKERY, CRR/RMR and Notary Public, hereby certify the witness was by me first duly sworn to testify to the truth; that the said deposition was recorded stenographically by me and thereafter reduced to printing under my direction; and that said deposition is a true record of the testimony given by said witness.

I certify the inspection, reading and signing of said deposition were NOT waived by counsel for the respective parties and by the witness; and that I am not a relative or employee of any of the parties, or a relative or employee of either counsel, and I am in no way interested directly or indirectly in this action.

Denise Dobner Vickery, CRR/RMR
Notary Public in and for the
District of Columbia

My Commission expires: February 28, 2023